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MARCH, 1929

ORIGINAL ARTICLES.

THE VALUE OF PHENYLHYDRAZINE IN THE TREATMENT OF POLYCYTHEMIA VERA.*

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The treatment of that form of polycythemia associated with chronic cyanosis and moderate enlargement of the spleen (erythremia; Osler's disease; Vaquez's disease) has not been entirely successful. Very little is known concerning the pathogenesis of this disease, save that the erythroblastic bone marrow usually shows hyperplasia. Because of this lack of knowledge therapeutists have been unable to attack the disease at its source. Treatment, for the most part, has been symptomatic, the available therapeutic measures having been directed either to a reduction in the number of circulating red blood corpuscles or to the inhibition of red blood-cell formation. The employment of such measures has been based on the knowledge that many of the symptoms of the disease—headache, vertigo, cyanosis, dyspnea—are in great part due to the mechanical stasis in the circulation resulting from the polyglobulism.

Many methods of reducing the total blood mass have been tried: venesection, irradiation of the long bones and spleen, and the administration of benzol, either alone or in combination with the Roentgen

* Read before the Medical Section at the Fifty-seventh Annual Session of the California Medical Association, Sacramento, April 30 to May 3, 1928.

ray. Venesection and irradiation are both temporary in their effect, whereas benzol combined with irradiation, although occasionally successful in producing a more or less permanently good effect[1] depress also the white blood-cell forming tissue of the bone marrow.

Within the last few years another drug—phenylhydrazine hydrochlorid—has found considerable favor in the treatment of polycythemia vera. It is the purpose of this report to record the clinical course of a patient with polycythemia vera treated with phenylhydrazine and to emphasize the value and dangers of this drug as well as the importance of certain criteria for the control of its dosage.

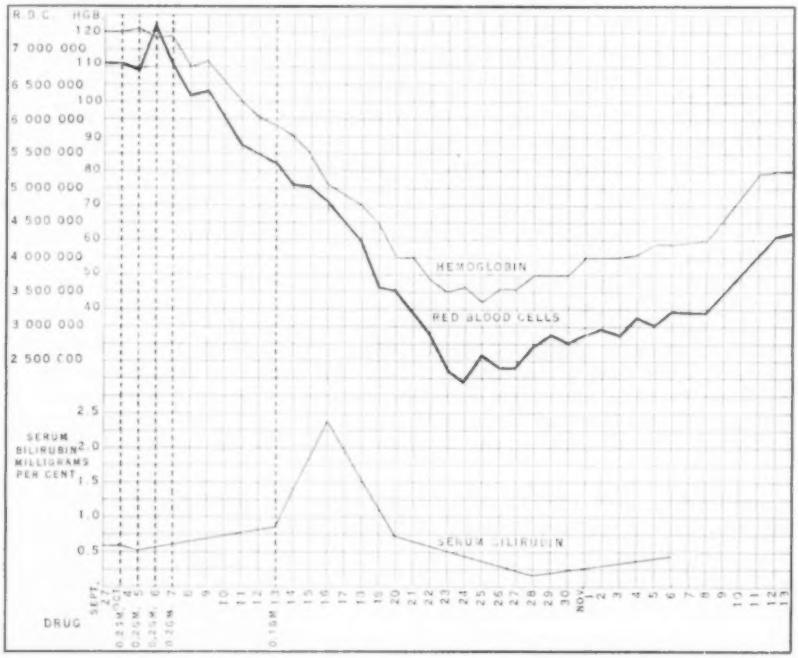
Phenylhydrazine. The formula for phenylhydrazine is $C_6H_5NH.NH_2$. It is prepared on a large scale from anilin and is used commercially for the production of antipyrin. When freshly distilled, phenylhydrazine is a colorless, highly refracting oil. On cooling it sets to a mass of tabular monoclinic crystals. Of the salts of phenylhydrazine, the hydrochlorid is the most important.

It has long been known that in large doses phenylhydrazine is a powerful protoplasmic poison, causing extensive fatty degeneration of the liver and marked destruction of red blood corpuscles. On hemoglobin it has a reducing effect, forming with it a green compound known as hemoverdin.

In 1908 Morawitz and Pratt[2] used phenylhydrazine to produce experimental anemia in animals. Eppinger and Kloss[3] ten years later, first tried the drug on patients with polycythemia vera. They observed a reduction in the amount of hemoglobin and in the number of circulating red blood cells, mild jaundice and a dark urine. Experimentally the drug has been administered mainly by the subcutaneous route, but its marked toxicity when so given precludes its injection in human beings. For clinical purposes phenylhydrazine hydrochlorid is given in capsules by mouth.

Patients appear to show marked differences in their response to phenylhydrazine. A dose of phenylhydrazine which in 1 patient will produce marked destruction of red blood cells will in another patient produce little effect. Thus in 2 of Owen's[4] patients, 1 required 2.6 gm. to reduce the blood count to normal, whereas another patient required almost twice the dose (4.3 gm.). The total amount of phenylhydrazine administered to the patients studied by Brown and Giffin[5] varied from 3.4 gm. to 7.6 gm. These doses are large in comparison with the small amount of the drug which gave rise to marked destruction of red blood cells and a hemolytic crisis in our patient (0.9 gm.). It is obvious therefore that no hard-and-fast rules as to dosage can be given. The plan of treatment outlined by Owen and others is safe. Guided by frequent blood examinations, treatment may be begun by giving 0.2 gm. daily for three or four days. The phenylhydrazine is given in capsules by mouth. After that the dose is reduced to 0.1 gm. daily until the leukocytes increase in number, or the hemoglobin falls

below 100 per cent. When this occurs 0.1 gm. may be given every second or third day or the drug may be stopped. It is probably safer to discontinue the phenylhydrazine for a few days after 1 gm. has been given, or even before that dose has been reached if there are indications of progressive blood destruction. The latter may continue for a week or ten days after the last dose has been given (Chart), and this cumulative effect should be taken into account in the practical use of this remedy. Should the hemoglobin and red blood corpuscles begin to rise above normal figures, the capsules may be started again or increased in frequency. It has been found



that about 0.1 gm. once a week will be sufficient in the average patient with polycythemia vera to keep the red blood-cell count within normal limits. By proceeding slowing in this way it is possible to obtain the maximum therapeutic effect with little if any danger to the patient.

Report of Case.—T. K., a married woman, aged forty-two years, first came under observation on September 23, 1926. At that time she entered Mount Zion Hospital, San Francisco, complaining of headache and inability to move her right arm. From that date until her final discharge from the hospital on November 14, 1927, a little over a year, the patient was under rather close observation both in the hospital and in the out-patient clinic.

There had been little illness in her family. The patient had lived in Poland until the age of twenty-nine years when she came to Stockton,

California. Except for occasional colds she had always been in good health until four weeks prior to her first admission to the hospital. Because of continued headaches, dizziness and some impairment in her vision she gave up her occupation of seamstress. About this time her friends commented upon the healthy deep red color of her cheeks and lips, although the patient herself showed increasing headaches, dizziness, fatigability and shortness of breath. For several weeks she was treated by her physician in a Stockton hospital for Bright's disease, a diagnosis made doubtless because of her persistent headaches, high blood pressure, albuminuria and a urinary sediment containing red blood cells and casts.

Four days prior to coming under our care she noticed tingling and numbness of the finger tips of the right hand and wrist drop.

On physical examination the most striking finding was the purplish red color of the cheeks, ears, nose and lips, and the engorgement of all the mucous membranes—buccal, nasal and pharyngeal. The conjunctivæ were also markedly engorged and the fundi showed black tortuous veins. Only a moderate hypertrophy of the left ventricle was made out. The blood pressure was 168 systolic and 104 diastolic. The liver edge was just palpable. Splenic dullness began in the sixth interspace and extended to the costal margin. The spleen was slightly palpable only on two occasions, once during the period of a hemolytic crisis to be commented upon later, and again during her short stay in the University of California Hospital in August, 1927. For this observation and for some of the data recorded in Table V we are indebted to the medical and roentgenological staffs of that institution.

The patient's hands were found to be very cyanotic. The right arm showed a paralysis of both the extensor and flexor groups of muscles. The reflexes were hyperactive and there was no loss of sensation.

The treatment consisted of three courses of phenylhydrazine, the total amount of the drug given being 1.9 gm., two courses of exposure to the Roentgen rays and one course of benzol treatment. The patient's response to these different forms of therapy and more particularly the effect of phenylhydrazine administration on the blood are recorded in the tables and chart.

Comment. The history and examination of this patient present several clinical features worthy of further comment. Splenomegaly was very slight, if present at all. It should be emphasized that although enlargement of the spleen was included in Osler's original definition of the disease, that it is to be made out in only a certain proportion of patients. It is not a constant clinical feature of the disease. Of 32 patients admitted to the Johns Hopkins Hospital in twenty-five years, Futcher[6] found the presence of a large spleen recorded in only 19 cases. Even in the absence of splenomegaly the general clinical manifestations of the disease and histologic examinations of the blood are sufficient for a correct diagnosis.

Hematuria may be a presenting symptom. When the urine shows also albumin and casts a diagnosis of Bright's disease is not infrequently made. In the case report it was noted that because of these abnormal urinary findings the patient had been treated for Bright's disease. Studies of renal function before and after clinical improvement and quantitative observations on the urinary sediments did not, however, justify such a diagnosis. The phenolsulphonephthalein elimination, although somewhat depressed when the

patient was acutely ill, soon returned to within comparatively normal limits after clinical improvement took place. The total and differential-cast counts made according to the method of Addis[7] over a period of six weeks (Table III) gave results which correspond in no way with those found by Addis in hemorrhagic Bright's disease. In the first instance the total cast count in the urinary sediment of the polycythemia patient during the stage of greatest vascular engorgement was only 350,000 for the twelve-hour period. Of this number 75 per cent were blood casts. At this same period the total number of red blood cells was 20,000,000. These figures do not correspond with Addis' figures for any stage of hemorrhagic Bright's disease. In this condition, as pointed out by Addis the total cast counts may number many millions in a twelve hour specimen of urine and the differential cast counts usually show a higher percentage of hyalin than red blood-cell casts. With the disappearance of the general vascular engorgement and the development of a phenylhydrazine anemia in our patient the hematuria and other abnormal urinary findings entirely disappeared (Table III).

The third interesting clinical manifestation noted in the history was the transient palsy of the right arm. Vascular lesions of the brain due to the formation of small thrombi are not uncommonly observed in polycythemia vera. Six of the 32 patients analyzed by Futcher had hemiplegias. Because of the slow development of these vascular complications they are thought to be due to cerebral thrombosis. These patients show also a great tendency to venous thrombosis. Varicose veins of the lower extremities and phlebitis are commonly noted in polycythemia vera patients. The occurrence of a thrombosis of the internal saphenous vein was a complication of phenylhydrazine administration in our patient. A similar complication is mentioned by Owen, and also by Brown and Giffin. The latter observers attribute it to excessive blood destruction and the liberation of thromboplastic material from the red blood cells and the blood platelets.

In Tables I and II are recorded the effect of phenylhydrazine on the blood of the patient studied. The dosage was controlled by frequent red and white blood-cell counts and by quantitative determinations of the serum bilirubin. The decisive effect of phenylhydrazine in destroying blood is evident from a study of these tables. Twelve days after beginning treatment the red blood corpuscles showed a reduction of several millions, the number of leukocytes had almost doubled and the amount of serum bilirubin had increased fourfold. Blood destruction continued for about ten days after the drug was stopped, the hemoglobin and red blood cells reaching the low levels of 46 per cent and 2,200,000 per cmm. respectively. This period of rapid blood destruction was characterized by an intensification of the jaundice, and the dark color of the urine, by enlargement of the liver and spleen, abdominal distress, nausea, anorexia

TABLE I.—THE EFFECT OF PHENYLHYDRAZINE ON THE HEMOGLOBIN, RED BLOOD CORPUSCLES, LEUKOCYTES AND SERUM BILIRUBIN IN POLYCYTHEMIA VERA.

Date.	Dose of phenylhydrazine (gm.).	Hemoglobin (Sahli).	Red blood cells (in millions).	White blood cells (in thousands).	P.M.N. (per cent).	Serum bilirubin (mg. per 100 cc.).	Remarks.
Sept. 23, 1926	....	120	7.0	26.0	90	.....	Blood pressure 168/104; phthalein 14 per cent in two hours.
Sept. 24, 1926	....	120	6.44	23.8	87	0.65	Fragility of red blood cells 0.5 per cent to 0.35 per cent NaCl.
Sept. 27, 1926	....	120	6.8	16.7	81	.....	
Oct. 4, 1926	0.2	120					
Oct. 5, 1926	0.2	121	6.7	20.0	80	0.52	Urine dark in color.
Oct. 6, 1926	0.2	118	7.29	23.3	90		
Oct. 7, 1926	0.2	119	6.75	24.9	87		
Oct. 8, 1926	....	110	6.3	25.0	92	.....	Thrombosis of popliteal vein.
Oct. 9, 1926	....	112	6.4	30.0	87		
Oct. 11, 1926	....	100	5.65	34.0	90	0.78	
Oct. 12, 1926	....	96	5.47	28.6	88		
Oct. 13, 1926	0.1	93	5.35	35.0	90	.....	Total dose of phenylhydrazine 0.9 gm.
Oct. 14, 1926	....	90	5.05	43.6	88	.....	Slight jaundice; urobilin in urine.
Oct. 15, 1926	....	85	5.0	60.7	90	.....	Intense jaundice.
Oct. 16, 1926	....	76	4.82	43.0	88	2.40	
Oct. 18, 1926	....	70	4.2	50.0	90		
Oct. 19, 1926	....	65	3.6	54.0	90	.....	Fragility of red blood cells 0.5 per cent to 0.35 per cent.
Oct. 20, 1926	....	55	3.5	49.3	84	0.76	Jaundice disappearing.
Oct. 21, 1926	....	55	3.2	55.2	87	.....	Polychromatophilia; stippled.
Oct. 22, 1926	....	48	2.9	56.8	83	.....	Central pallor of red blood cells; occasional myelocyte.
Oct. 23, 1926	....	45	2.34	41.5	82		
Oct. 24, 1926	....	46	2.2	44.5	80	.....	Blood pressure 95/60.
Oct. 25, 1926	....	42	2.59	39.3	86	.....	Fragility of red blood cells 0.45 per cent to 0.35 per cent.
Oct. 26, 1926	....	46	2.39	34.3	85	.....	Phthalein elimination 27 per cent in two hours.
Oct. 27, 1926	....	46	2.41	39.5	82		
Oct. 28, 1926	....	50	2.71	30.0	84	0.204	
Oct. 29, 1926	....	50	2.88	27.4	85		
Oct. 30, 1926	....	50	2.74	31.0	86		
Nov. 1, 1926	....	55	2.9	28.15	84		
Nov. 2, 1926	....	55	2.99	28.5	83		
Nov. 3, 1926	....	55	2.9	28.8	82	.....	Blood pressure 95/60.
Nov. 4, 1925	....	56	3.11	29.7	82		
Nov. 5, 1926	....	59	3.07	25.6	84		
Nov. 6, 1926	....	59	2.22	23.8	84		
Nov. 8, 1926	....	60	3.2	19.6	77	0.47	Blood pressure 100/60; phthalein elimination 62 per cent in two hours. Patient discharged from hospital.

Patient discharged from hospital.

TABLE II.—THE EFFECT OF FURTHER DOSES OF PHENYLHYDRAZINE ON THE BLOOD IN POLYCYTHEMIA VERA.

Date.	Dose of drug (gm.).	Hemoglobin (Sahli).	Red blood cell (in millions).	White blood cell (in thousands).	P.M.N. (per cent).	Remarks.
Nov. 12, 1926	....	79	4.09	16.0	73	
Nov. 16, 1926	....	80	4.3	18.0	73	
Nov. 20, 1926	....	80	4.32	16.0	80	Blood pressure 110/80.
Dec. 20, 1926	....	115	6.65	26.0	84	Paresis of right arm much improved; blood pressure 150/80.
Feb. 11, 1927	....	120	6.15	28.3	87	
Feb. 12, 1927	....	120	6.24	22.4	90	
Feb. 15, 1927	....	115	6.1	22.4	88	
Feb. 17, 1927	0.2					
Feb. 26, 1927	0.2	110	6.22	28.6	..	Blood pressure 120/90; dizziness less marked.
Mar. 12, 1927	....	85	5.33			
Mar. 19, 1927	....	80	4.9	28.5	..	Blood pressure 105/85; complains of weakness.
May 24, 1927	....	120	6.83	21.5		
Oct. 13, 1927	0.1	....	....	....	..	Blood pressure 130/110.
Oct. 14, 1927	0.1					
Oct. 15, 1927	0.1	105	7.05			
Oct. 16, 1927	0.1					
Oct. 17, 1927	0.1					
Oct. 10, 1927	0.1	105	5.75			
Oct. 19, 1927	0.1					
Oct. 20, 1927	0.1					
Oct. 21, 1927	0.1					
Oct. 22, 1927	0.1	105	5.45			
Oct. 23, 1927	0.1	....	....	....	..	Total of 1.2 gm. phenylhydrazine given in twelve days.
Oct. 24, 1927	0.1					
Oct. 25, 1927	....	95	5.0	....	..	Slight icterus of skin and sclerae.
Oct. 28, 1927	....	85	4.82			
Oct. 30, 1927	....	80	3.45			
Nov. 4, 1927	....	65	3.25	..	..	Blood pressure 140/70.
Nov. 8, 1927	....	50	2.4			
Nov. 11, 1927	....	52	2.5			
Nov. 14, 1927	....	64	3.0	20.0	80	Headache and dizziness much improved.
Dec. 6, 1927	....	86	5.36	19.4	87	
Jan. 18, 1928	....	70	6.512	24.8	84	Blood pressure 134/100.

TABLE III.—THE EFFECT OF PHENYLHYDRAZINE TREATMENT ON THE URINARY SEDIMENT OF A PATIENT WITH POLYCYTHEMIA VERA.

Date.	Dose of drug (gm.).	Blood.		Urine.					
		Hemoglobin (Sahli).	Red blood cells (in millions).	Total casts (no. in 12-hour urine).	Blood casts (per cent).	Granular casts (per cent).	Hyalin casts (per cent).	Red blood cells (millions in 12-hour urine).	Albumin (gm. per 1000 cc.).
Sept. 23, 1926	....	120	7.0	350,000	75	25	..	20	0.4
Sept. 24, 1926	....	120	6.44	300,000	80	20	..	21	0.4
Oct. 4, 1926	0.2	120	....	60,000	55	45	..	8	0.5
Oct. 5, 1926	0.2	121	6.7						
Oct. 6, 1926	0.2	118	7.29	90,000	35	50	15	2	0.2
Oct. 7, 1926	0.2	119	6.75						
Oct. 9, 1926	....	112	6.4	180,000	30	55	15	5	0.2
Oct. 13, 1926	0.1	93	5.35						
Oct. 14, 1926	....	90	5.05	110,000	55	45	..	23	0.1
Oct. 18, 1926	....	70	4.2	110,000	55	45	..	11	trace
Oct. 21, 1926	....	55	3.2	9,000	..	..	..	0.4	trace
Oct. 27, 1926	....	46	2.41	21,000	25	65	10	0.5	0
Oct. 28, 1926	....	50	2.71	11,000	10	80	10		
Nov. 1, 1926	....	55	2.9	5,000	30	50	20	0.1	0
Nov. 6, 1926	....	59	2.22	4,300	..	60	40	0	0
Nov. 8, 1926	....	60	3.2	4,000	..	55	45	0	0

TABLE IV.—THE EFFECT OF BENZOL ON THE BLOOD IN POLYCYTHEMIA VERA.

Date.	Dose of benzol (gm.).	Hemoglobin (Sahli).	Red blood cells (in millions).	White blood cells (in thousands).	P.M.N. (per cent).	Remarks.
Aug. 30, 1927	3	110	6.45			
Aug. 31, 1927	3	110	6.13			
Sept. 1, 1927	3					
Sept. 2, 1927	3	105	6.0			
Sept. 3, 1927	3					
Sept. 4, 1927	3					
Sept. 5, 1927	3	107	6.3	24.9	90	
Sept. 6, 1927	3					
Sept. 7, 1927	3	104	6.08			
Sept. 8, 1927	3	107	6.2	26.9	87	
Sept. 9 to 25, 1927	3 daily	....	....	....	..	Total of 81 gm. benzol given in twenty-seven days.
Sept. 26, 1927	....	110	6.2	24.0	..	Condition unchanged.

TABLE V.—THE EFFECT OF ROENTGEN RAYS ON THE BLOOD IN POLYCYTHEMIA VERA.

Date.	Roentgen rays skin erythema dose.	Hemoglobin (Sahli).	Red blood cells (in millions).	White blood cells (in thousands).	P.M.N. (per cent).	Remarks.
July 13, 1927	1/10	150	5.9	38.0		
July 15, 1927	....	160	6.67	28.4		
July 20, 1927	....	140	7.77	20.8		
July 27, 1927	1/10					
Aug. 2, 1927	....	150	8.7	24.3		
Aug. 4, 1927	1/10	147	8.16	20.4		
Aug. 6, 1927	....	130	7.51	23.75		
Sept. 26, 1927	....	110	6.2	24.0	86	
Sept. 27, 1927	1/4					
Sept. 29, 1927	....	115	6.5	23.0		
Oct. 9, 1927	....	110	6.53			
Oct. 10, 1927	1/3					
Oct. 11, 1927	....	110	5.85	13.0	..	Considerable reduction in white blood cells; very slight reduction in red blood cells; clinical condition unchanged.

and marked weakness. Several months after this stormy hemolytic crisis examination of the blood showed a return to the same high figures for hemoglobin, red cells and leukocytes noted prior to the beginning of the phenylhydrazine treatment.

Little comment need be made on the effect of benzol and irradiation upon the blood in polycythemia vera. Many such observations have been recorded in the literature during the past ten years. Table IV shows clearly that 81 gm. of benzol given over a period of twenty-seven days produced no change in the hemoglobin, red blood cells and leukocytes of the patient studied. Similarly, five exposures of the spleen to the Roentgen rays in moderately large doses gave rise to a very slight reduction in red cells and the usual fall in the leukocyte count. It should however be emphasized that the combined treatment—benzol and irradiation—does in certain instances produce a striking effect.[1] This form of therapy was not carried out in this instance, nor did we have a suitable opportunity to try the value of giving phenylhydrazine combined with Roentgen ray exposures. This method of treatment should be considered because phenylhydrazine is not leukotoxic and in combination with the Roentgen rays might possibly be useful in smaller dosage.

Conclusions. Phenylhydrazine hydrochlorid produces definite clinical improvement in the patient with polycythemia vera. The drug is worthy of being given a trial if the dangers of its use be kept in mind. Guided by frequent counts of the red and white blood corpuscles and by estimations of the serum bilirubin, one may give phenylhydrazine without danger to the patient. It is wise to stop its administration before the red blood count reaches a normal level because its action continues after its withdrawal. The hemolytic crisis observed by others and ourselves may be avoided if additional safeguards be used. Because of the great difference in the response of patients to varying amounts of the drug, quantitative determinations of the serum bilirubin and frequent leukocyte counts should be made. A marked rise in the amount of serum bilirubin means excessive blood destruction, whereas a rising leukocyte count probably indicates great destruction of liver cells.

Finally, it may be stated that the use of phenylhydrazine is no exception to the general observation that the various measures used in the treatment of polycythemia vera are transitory and the effect produced purely palliative. General experience seems to show that no matter what therapeutic measure is adopted there is a tendency for the red blood-cell count to rise and for the subjective symptoms to return.

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EFFICIENCY OF THE MECHANICAL FACTORS OF RESPIRATION.

A Study of Respiratory Reserve.*

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In a series of experiments[5] previously reported an effort was made to determine the effect of phrenic neurectomy on respiration. It was concluded that either unilateral or bilateral phrenic neurectomy was attended with slight risk and did not produce demonstrable impairment of function in general or of respiratory function in particular. Compensation was sufficient to overcome the loss in function of half or the whole diaphragm of the dog and the animal was able to carry on its usual activities without embarrassment or dyspnea. This led to the consideration of the alternative, that compensation is a powerful factor in maintaining the respiration or that the value of the diaphragm as a respiratory muscle has been greatly overestimated. After completion of this work I became aware that similar experiments on the diaphragm had been conducted on the horse and that the results were exactly the same as I had obtained on the dog. I have observed, moreover, that unilateral phrenic neurectomy is not attended with any great danger to man, that his vital capacity is not materially decreased, and that the movements of the wall of the chest are not disturbed by this operation. Instances have been reported of bilateral phrenic neurectomy successfully accomplished in man and not productive of untoward symptoms.[1,2,3]

I have confirmed these observations by examining patients having true unilateral eventration of the diaphragm and congenital absence of the hemidiaphragm, and after paralysis of half of the diaphragm by evulsion of the phrenic nerve. Lord and Lewald have reported their observations under similar conditions.

Study of comparative anatomy lends color to the belief that the primary function of the diaphragm is to make possible an increase

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in intracolonic pressure and that its respiratory function is secondary to this primary purpose. Jones has carefully considered this conception of its development and purpose. My observations led me to believe that respiration is a complicated mechanism made up of the combined movements of various sets of muscles, each so controlled that coördination of movement is maintained, yet each so independent that it may be placed in dysfunction without disturbing either the single or combined action of the others.

As the former study was confined to the effect produced by the loss of only one set of muscles, it became necessary to study the effect when other sets of muscles were made functionless either alone or with unilateral or bilateral paralysis of the diaphragm. The intercostal muscles have been accepted as important muscles in respiration and are easily studied. They can be paralyzed (in part) in experimental animals by cutting the intercostal nerves, and the number of muscles placed in dysfunction can be controlled by the experimental requirements.

The effect on the respiration of loss of variable numbers of intercostal muscles, and, after repeated operations to determine, if possible, the effect of loss of all the intercostal muscles, seemed, therefore, a desirable study. When this was accomplished, paralysis of the intercostal muscles could be combined with phrenic neurectomy until the limits of respiratory efficiency could be determined. It seemed probable that such limits would be reached before all of the intercostal muscles and the whole diaphragm could be rendered paralytic. This is equivalent to a study of respiratory reserve from the standpoint of the neuromuscular apparatus. The effect of the different operations on the movements of the wall of the chest, on intrapleural tension and on the animal's ability to maintain efficient vital capacity was also included in this study. Relative to the latter function, the animal's reaction to exercise and the measurement of the volume of air breathed in a unit of time were noted. Only four animals were used in this experiment, because of the difficulties in training them for observation with a spirometer.

Method of Investigation. The animals were examined by the familiar methods of clinical practice, inspection and palpation being chiefly relied on to detect variations from the normal. To confirm the observations made from clinical examination, the animals were placed in a special frame and synchronous kymographic records made of bilateral thoracic movement indicating the equality or inequality of respiratory excursions. The apparatus was the same as that described elsewhere.[5] Intrapleural tension was determined on anesthetized animals under varying circumstances during the several operative procedures. They were examined fluoroscopically and finally at necropsy.

Results. *Group I. Effect of Sectioning from Six to Twelve Intercostal Nerves.* On the day following operation the animals were lively

and did not show evidence of cyanosis or of respiratory embarrassment. When they were on the observation table it could be seen that the lower portion of the chest on the side of operation moved less freely than the similar portion on the normal side. When the thorax was at rest it appeared symmetrical; on inspiration the costal margin on the side of the operation was not drawn toward the midline but moved outward through a reduced excursion of variable degree. Although the difference was always apparent on inspection, it was sometimes too small to be recorded by the kymograph; in other cases a loss of as much as 50 per cent of the normal excursion was recorded; the loss depended on the extent of the operative procedures. It was observed that the upper part of the abdomen moved less than normally and the rectus muscle on the side of operation had lost its tone and was flaccid. The lower portion of the abdomen, however, moved normally and the tone of the muscles seemed normal. On succeeding days with a certain number of dogs the variation of the latitude of movement of the wall of the chest from normal became increasingly less until a difference in the excursion of the two sides could not be observed, nor could a difference in amplitude of the outward movement of the costal arches be observed or discovered by actual measurement.

The intrapleural tensions were equal bilaterally and within normal limits. When the chest was examined under the fluoroscope the illumination of the normal side was more complete than that of the other. During the next few days such differences could not be detected; the lungs were equally illuminated during inspiration.

A definite explanation cannot be given for the early loss of function and the prompt return to normal conditions. The effect of operative trauma, the initiation of movement by the upper intact muscles and the reserve action of accessory muscles must all play a part in compensating for lost function. Certainly the outward bulging flank and the reduced excursion of abdomen and thorax had disappeared by the time the wound was healed and the animal was to all intents and purposes normal and could enjoy normal exercise without dyspnea or cyanosis.

In an exceptional dog on which the operation had included more than six intercostal nerves, compensation was not so thorough. Months later the side operated on, including the chest and the abdomen, bulged outward. Moreover, the upper intercostal spaces were drawn inward with inspiration. The indrawn interspaces reflected the influences of the negative intrapleural pressure. The effect is comparable to the phenomenon known as Litten's sign, which is produced when the diaphragm descends and draws away from the parietal pleura. It is also similar to the paradoxic movement of the chest proper which will be considered later in a discussion of the effects produced by transection of the spinal cord. Among the dogs in which all the intercostal nerves had been severed

on one side the restoration of movement was neither complete nor frequent. Bulging of chest and flank was never constant, but the limitation of movement of the costal arch maintained nearly the primary loss of approximately 50 per cent of normal excursion. Even when the degree of excursion seemed to be almost completely regained the movement was not produced by muscles capable of exerting the same degree of force to counteract resistance.

In all the animals studied, regardless of the number of intercostal nerves sectioned the respiratory and pulse rates remained normal; the vital capacity was so little disturbed that dyspnea and cyanosis did not occur in a single instance. The animals played about and could not be distinguished from their normal mates.

Group II. The Effect of Sectioning All Intercostal Nerves. As unilateral intercostal neurectomy did not disturb respiration, it was decided to choose one of the dogs that had undergone this procedure and cut as many nerves as possible on the other side. The operation was much less formidable than was anticipated. It became possible to cut all of the twenty-four intercostal nerves in two stages without undue operative shock or disability. When only one side was operated upon asymmetry in movement was observed, with a reduction of 50 per cent of the movement on this side. If the wall of the chest was thin there was a definite retraction near the costochondral juncture during inspiration. With both sides paralyzed the respiratory movements were symmetrical. Observations, measurement and kymographic readings, all demonstrated the curious phenomenon of outward movement of the paralyzed chest during inspiration. The fluoroscope demonstrated that the movement of the diaphragm remained undisturbed. The converse of my former observations is true, that is, that animals having control of only diaphragmatic and accessory respiratory muscles have normal respiratory capabilities and can survive without discomfort the same tests of endurance as animals that have suffered complete loss of diaphragmatic function and that animals maintain respiratory competency, even though deprived of function in the intercostal muscles or in both halves of the diaphragm.

Group III. Effect of Sectioning Intercostal and Phrenic Nerves. It has just been shown in Group II by section of all the intercostal nerves and is to be shown in Group IV by transection of the spinal cord that a dog can live without respiratory embarrassment under these conditions—in the latter case for only a few days and in the former for an indefinite period. The next investigation concerned the respiratory efficiency after both intercostal and phrenic nerves had been sectioned.

Animals, in which from ten to twelve intercostal nerves had been cut on one side, were operated on again within a month and the phrenic nerve on the same side was severed. The animals were observed under the same conditions as in the other experiments.

They played normally; respiratory and pulse rates were normal. There was evidence, both on inspection and on actual measurement, of diminished outward excursion during inspiration in the animals

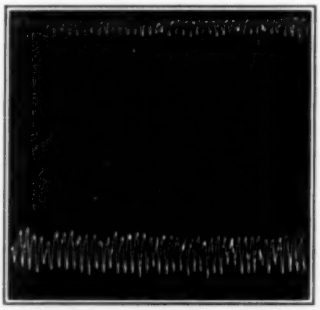


FIG. 1.—*Immediate result.* Normal functional activity with normal pulse and respiratory rate and normal temperature. The chest remained symmetric but outward movement during inspiration was reduced to half. The kymographic tracing illustrates a reduction of 50 per cent. Tracing made at the level of the ensiform. *Late result.* Left side of the chest bulged outward. Reduction of movement was permanent. Upper abdominal muscles were flaccid on the left side and the flank sagged. Subcostal angle remained normal. Reading taken at the level of the ensiform.

in which the ten lower left intercostal nerves and the left phrenic nerves had been cut. In one animal the unaffected side moved outward 4.75 mm. and the side operated on moved through an

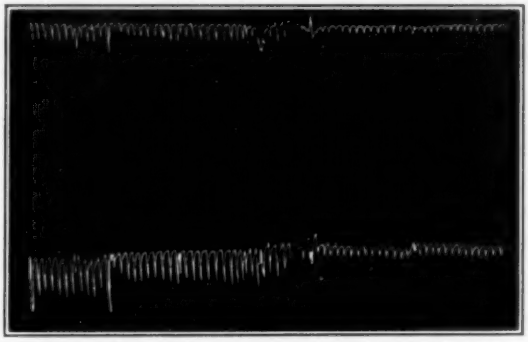


FIG. 2.—The tracings show the movements of the chest at both the ensiform and costal margin levels. Normal functional activity. Side operated on bulges outward and movement during inspiration is reduced. Movement on affected side acts less vigorously against resistance. Left side of diaphragm was high in the thorax and moved in a paradoxic direction.

excursion of only 1.58 mm. The extent of the motions was variable but the most common are given. The costal margins and flank on the side operated on are flanged outward, making the chest and abdomen asymmetric. The abdominal muscles on this side

were flaccid. The depth of inspiration was increased, even though the rate was unchanged.

Kymographic records made at the two levels chosen as a routine confirmed the clinical observations, while fluoroscopic examination demonstrated paralysis of the hemidiaphragm. It was high in the thorax and the movement, if any, was paradoxic.

The opposite phrenic nerve was separated a week later and again the animal was able to compensate for lost function; respiration was maintained without evidence of distress. The animals played energetically and were not dyspneic. Respiratory and pulse rates were normal.

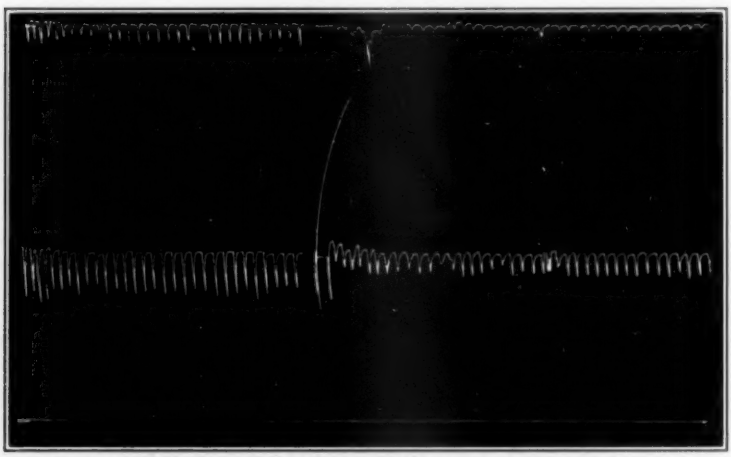


FIG. 3.—Tracings made twelve days later showing the movement of the chest following bilateral phrenic neurectomy. The reduced movement remained on the side of the paralyzed intercostal muscles. Comparison shows how little movement is influenced by loss of diaphragmatic contraction.

The movements of the upper portion of the chest were equal bilaterally, but the side on which the intercostal muscles and hemidiaphragm were paralyzed had lost almost all its outward movement at and below the level of the ensiform process. This was confirmed by both measurement and kymographic readings. In every experiment the intrapleural tension remained bilaterally equal and within normal limits regardless of the type or extent of the operation. The fluoroscopic examination revealed typical evidence of complete paralysis of the diaphragm. The animals played and were energetic, although they had lost the function of from ten to twelve intercostal muscles on one side, as well as both sides of the diaphragm.

An attempt was next made to determine the number of intercostal muscles that could be paralyzed on the opposite side. In the first

experiment it was possible to cut the lower eight nerves so that ten intercostal muscles on the left, eight intercostal muscles on the right and both halves of the diaphragm were paralyzed. Anesthesia was attended with danger for the first time in this experiment. With the dog's recovery from the anesthetic respiratory competency soon developed. The next day he was active, playful and did not seem even slightly dyspneic. The asymmetry which was noted after only one thoracic operation now disappeared. One phenomenon was peculiar and difficult to explain; the thoracic wall and the costal arches moved outward during inspiration.

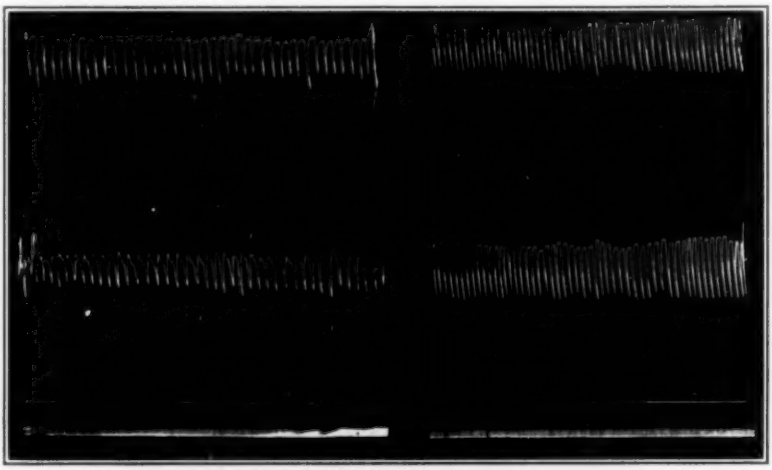


FIG. 4.—Tracings taken at the level of the ensiform. Symmetry returned with bilateral intercostal and diaphragmatic paralysis. Dogs functionally competent but vital capacity much reduced. Dog was unable to survive ether anesthesia. Trophic ulcer developed on sternum.

Animals whose intercostal muscles on one side had been paralyzed were next examined. At suitable intervals three separate operations were performed. All of the nerves of the intercostal muscles of the remaining side were severed at the first operation; one phrenic nerve was cut at the second and the remaining nerve at the third. It was considered improbable that animals could maintain respiratory competency at the conclusion of all three operations.

When all the intercostal nerves were sectioned the dog did not give any evidence of dyspnea; pulse and respiratory rates remained normal. The diaphragm moved normally; the costal arches moved outward with each inspiration. When all the intercostal nerves and one phrenic nerve were sectioned the dog was still able to run up and down stairs without dyspnea. The amplitude of movement on the two sides, as determined by actual measurement, was bilaterally equal.

The final operation was carried out with considerable misgiving. The dog became dyspneic while under the influence of the anesthetic, and after section of the remaining phrenic nerve he was forced to employ every available muscle about the head, neck and shoulders to expand the chest. The lower portion of the thorax was drawn inward with the inspiratory effort. By the following day he had accommodated himself to the loss, and the whole chest moved outward with inspiration. The muscles of the shoulder and neck were employed in respiration and the abdominal muscles were forcibly contracted with every expiration.

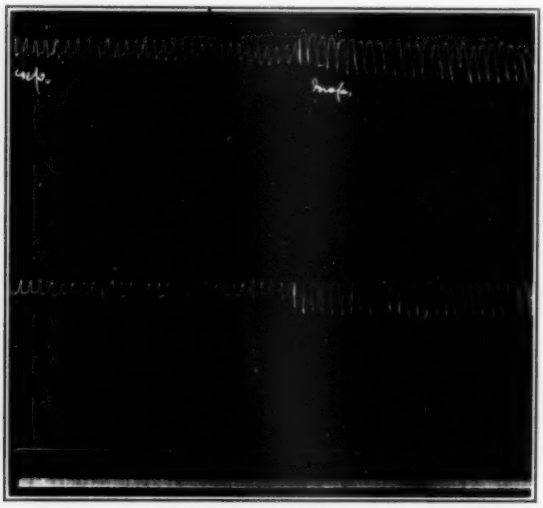


FIG. 5.—Paradoxic movement well illustrated by the tracing made at the level of the ensiform. Normal outward movement shown in the tracing made of the excursion of the costal arch. This movement was the result of the descent of the diaphragm. Vital capacity was competent to provide tidal air only.

The upper part of the abdomen and the whole wall of the chest was anesthetic and a trophic ulcer formed over the sternum. The outward movements were proved to be bilaterally equal by inspection, kymographic record and measurement. The outward excursion was 4.75 mm. on each side. Fluoroscopic examination proved that the diaphragm was paralyzed. The vault was high on both sides and appeared immobile.

Eight days later an attempt was made to anesthetize the dog in order to determine the intrapleural tension. This, however, was not accomplished as the dog became dyspneic, cyanotic and unable to provide himself with sufficient air; artificial respiration was necessary to resuscitate him.

Group IV. Effect of Transection of the Spinal Cord. In order to make sure that all the intercostal and abdominal muscles could be

paralyzed the spinal cord was severed at different levels in a series of animals. The results were similar to those of fracture of the cervical spine in man; the diaphragm alone or with accessory muscles should carry on respiration in experimental as well as in traumatic cases.

If the cord was severed at the level of the seventh cervical vertebra the wall of the chest became almost motionless. Any slight movement that occurred was seen best at the costal arch; it was directed outward from the midline during inspiration. The pulse and the respiratory rates were normal and there was no evidence of respiratory embarrassment. The upper part of the chest along the line of attachment of the ribs and the costal cartilages developed a paradoxic direction of excursion during inspiration. This portion moved toward the midline on inspiration and fell outward during expiration. The abdominal movements showed much less alteration. Normal rhythm and amplitude were maintained and the slow regular movements of the diaphragm could be observed with the fluoroscope. The vital capacity was not reduced sufficiently to cause dyspnea; the animal maintained sufficient respiratory competency to provide himself with tidal air. If the transection was made at higher levels the results were similar but usually more marked, so that at the level of the fifth cervical vertebra dyspnea actually was observed with characteristic alinasal movement, backward movement of the head and contraction of the muscles of the lip at the angle of the mouth. At or above the level of the fourth cervical vertebra transection produced almost immediate death. The animal made a great effort to obtain sufficient air by putting into use all the muscles still available. At this level the diaphragm and intercostal abdominal and shoulder-girdle muscles were functionless, and the remaining muscles did not retain sufficient function to maintain respiration. The brachial plexus in dogs arises from ventral branches of the fifth, sixth, seventh and eighth cervical and first thoracic nerves. The root supplied by the fifth cervical nerve is very small (Sisson).

Kymographic records not only confirmed the results of general examination, but graphically illustrated a peculiarity of expiration not observed in experimental animals of any other series. They showed that expiration was not a process as slow or slower than inspiration, but a sudden snapping back of the chest to the position of rest. Inspiration was effected by the muscular effort of the diaphragm and those accessory muscles having their innervation above the point of transection. Expiration was not any longer a muscular act, timed and prolonged by muscle tone and muscular contraction, but had become passive and as swift and sudden as the fall of a paralyzed arm which has been elevated and released.

In man, fractures of the neck usually occur at the level of the sixth cervical vertebra. Four patients with such a fracture have

been studied. Their respiratory movements corresponded exactly with those of the experimental animals in this series. Respiration was carried on by the action of the diaphragm, assisted perhaps by muscles receiving innervation above the point of cervical fracture.

The descent of the diaphragm increased the long diameter of the thorax and the negativity of intrapleural pressure, retracted the upper portion of the chest, increased intraäbdominal pressure and pressed outward the unresisting abdominal wall and thoracic arch.

One of the dogs previously examined whose diaphragm was paralyzed from phrenic neurectomy was operated on. The spinal cord was transected between the sixth and seventh cervical vertebræ. All the muscles innervated from below that level were paralyzed. Therefore, the animal could move its head and neck and retained slight control over the forelegs. The abdominal muscles were soft and atonic, but abdominal movement was normal in direction and extent. Movements in the upper part of the chest were limited and paradoxic, but the costal arches moved in a normal direction and through a normal excursive distance. The chest appeared symmetric and the costal-arch movement was proved symmetric by measurement of expansion. Kymographic records of the two sides were so nearly the same that the movements were believed to be equal.

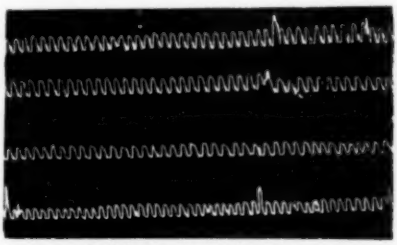
On fluoroscopic examination the left hemidiaphragm descended vigorously through a normal excursive distance with each inspiration. The right hemidiaphragm moved slightly in the opposite direction. The abdominal and intercostal muscles were paralyzed; therefore, abdominal movement and movement of the costal arches must have been passive and brought about by contraction of half of the diaphragm and the resultant pressure on the abdominal contents distributed equally in all directions. No experiment could illustrate more graphically Nature's liberal provision for maintaining one of the fundamental functions of the body. When all but a fraction of its ordinary mechanical equipment was lost the physiologic reserve still remained competent and provided adequate ventilation as long as the animal was at rest.

Intrapleural Tension. Repeated references have been made in this paper to observations on effect of various operative procedure on intrapleural tension. It is necessary only to summarize these observations, and this can be done by stating that the operative procedures did not cause any observable departure from normal or any observable difference in the two sides.

The Measurement of the Intake of Air Each Minute. As alterations from normal noted only in two dimensions, transverse and anteroposterior, seemed to be insufficient, it became necessary to devise a method to determine variations in all three dimensions, which is equivalent to an estimation of volume displacement. Several methods were considered, but the measurement of the intake of air each minute seemed most suitable.

RESPIRATORY EFFICIENCY IN THE DOG UNDER NORMAL CONDITIONS AND WITH VARIOUS MUSCLES INCAPACITATED.

Normal Dog K54. Weight, 5.7 kg.			Normal Dog K156. Weight, 15 kg.			Dog K156 (April 11, 1927). Weight, 13.3 kg.		
Pulse rate.	Respiratory rate.	Ventilation, liters each minute.	Pulse rate.	Respiratory rate.	Ventilation, liters each minute.	Pulse rate.	Respiratory rate.	Ventilation, liters each minute.
80	12	0.99	72	9	3.12	73	11	2.62
69	12	1.05	95	14	3.65	71	10	2.52
61	10	0.97	93	12	3.32	66	10	2.48
72	13	1.16	65	14	2.64	71	10	2.49
61	11	1.08	..	..	..	Intercostal nerves cut on both sides; one phrenic nerve cut.		
69	10	1.08	..	..	..			
*Transection of cord between sixth and seventh cervical vertebræ. Dog K28. Weight, 6.4 kg.			Intercostal nerves cut on left side. Dog K156. Weight, 14.6 kg.			Intercostal nerves cut on both sides; both phrenic nerves cut. Dog K156 (April 15, 1927). Weight, 13.2 kg.		
95	16	2.09	86	13	3.18	64	16	3.34
87	15	1.77	79	11	2.76	78	16	2.94
90	14	1.73	77	11	2.72	70	15	3.04
85	14	1.45	81	13	3.65	75	16	3.35
89	14	1.76	..	..	..			
90	14	1.64	..	..	..			
91	14	1.67	..	..	..			
86	14	1.67	..	..	..			
*Transection of cord between sixth and seventh cervical vertebræ Dog J910. Weight, 6.3 kg.			Intercostal nerves cut on both sides. Dog K156. Weight, 14 kg.					
63	13	1.01	97	15	3.62			
67	14	1.05	89	15	3.75			
69	14	1.12	83	14	3.95			
69	14	1.14	101	16	3.91			



Satisfactory type of tracing.

* Right phrenic neurectomy previously.

For several weeks before operation four dogs were trained to lie quietly wearing a mask and breathing through a gasometer. The training is tedious, but finally the dog remains quiet during the period necessary to make the measurements of the intake of air for each unit of time. In these experiments only the respiratory and pulse rates, the temperature and the volume of air inhaled were noted. Records were made before and after each operation (tabulation). This is a functional test and, like those for other organs of the body, such as the liver and kidney, it fails to register variations from normal until physiologic reserve is almost exhausted and obvious deficiency develops.

The second part of the experiment deals with animals in which transection had been performed. Three animals of the same weight

were observed, one a normal animal as a control, one in which transection of the cord only had been performed and the other in which transection of the cord and right phrenic neurectomy had been performed. The volume of air for each minute varied with the size and weight of the dog, but remained in all instances the same as in the control experiment. From this it appears that the animals that have lost the use of most of the intercostal muscles and of both phrenic nerves or of all but a few accessory muscles and half of the diaphragm not only lived but used the same amount of air for each unit of time as normal animals of the same weight. In all the animals the vital capacity was greater than the requirements of tidal air. In some animals the difference between vital capacity and tidal air was slight; this was particularly true of the animal in whom the cord and one phrenic nerve had been severed. A reading could not be made at first on this animal because the increase of dead space produced by the wearing of the mask made respiration impossible. A similar observation was made on an animal in which twenty-two of the intercostal nerves and both phrenic nerves had been cut. Although he was able to run up and down stairs without embarrassment, the vital capacity was not sufficient to provide him with tidal air when an attempt was made to use ether anesthesia. In both instances artificial respiration was required to preserve life.

Report of Necropsies. At various intervals from two to three months after the first operation the animals were killed by etherization. The wall of the chest was cleared of tissue down to the ribs where it became evident that the muscles which had been paralyzed differed markedly from their normal mates. They were thin, pale and translucent and did not fibrillate. They did, however, retain the ability to contract on direct stimulation and on contraction they forced the rib below to move in a normal inspiratory manner. The rib above was pulled downward, but the rib below the stimulated muscle moved upward and outward.

The normal intercostal muscles were thick, dark red and opaque. They fibrillated briskly and contracted promptly on direct stimulation, forcing the rib below the contracting muscle through a normal inspiratory movement. Movement was much more prompt and of greater amplitude than on the paralyzed side. The muscles of the upper abdominal wall on the side of the operation were also thin, pale and translucent, in marked contrast to those of the lower part of the abdomen or of the normal side. Before the abdomen was opened they did not offer resistance to palpation; the solid organs, such as the liver and spleen, could be palpated with ease.

After a small opening had been made into the abdominal cavity a lobe of the liver was drawn through and downward. This served to lower the level of the diaphragm and made it possible to see the

effect on the wall of the chest, the costal arch and the costal margin. Various levels could be attained in the descent and the effect on the wall of the chest was observed at each level. As a result the wall of the chest in its entire length was forced into a position of expiration at all levels and the amplitude of movement was greatest opposite the ensiform level. The effect was much less at the costal margin.

When the thoracic cavity was opened the line of demarcation between normal and paralyzed muscle was apparent and corresponded to the scarring produced at the point where the nerve was sectioned. The paralyzed muscles were similar to those already described.

The intercostal nerves were dissected away from the margin of the rib and the normal proximal end was found embedded in a neuroma that connected it with the attenuated distal end. It was proved in one instance, in which it was thought that ten intercostal nerves on one side and eight on the other had been sectioned, that only nine and seven nerves, respectively, had been severed. In another instance in which all twenty-four intercostal nerves had been operated on the first nerve on both sides had escaped section. In another the seventh intercostal nerve had not been sectioned. The corresponding muscles stood out in marked contrast to the adjacent paralyzed muscles. In the animals in which the phrenic nerves had been cut the condition of the nerve and of the diaphragm was the same as that described in a former study.[5]

The heart, lungs, pleura and abdominal organs were normal in all the animals examined.

Microscopically the paralyzed muscles appeared atrophic. The fibers were shrunken, deeply stained, retained their striation and, on account of the greatly increased number of fibers in the microscopic field, the number of nuclei appeared to be increased.

The peripheral ends of the sectioned nerves were also shrunken, the axis cylinders had disappeared, the myelin was absorbed and a proliferation of nuclei was seen in the sheath of Schwann. The spinal cord at the point of transection was softened and necrotic; sections made above and below the level of transection gave early evidence of ascending and descending degeneration. The dog was killed too soon to show gross degenerative changes in the muscles in which the cord had been transected.

Summary and Conclusions. The chief observations regarding the movements of the wall and the chest and of the costal arch were briefly: (1) When intercostal nerves have been sectioned on one side the wall of the chest moves outward normally, but with limited excursive distance during inspiration; (2) when the spinal cord has been transected the upper portion of the wall of the chest moves toward the midline during inspiration; this paradoxic movement

was noticed in every animal and was similar to the movement of the chest at necropsy when the diaphragm is drawn downward; (3) when the spinal cord has been transected the costal arches move outward normally and equally; (4) when the spinal cord has been transected and one phrenic nerve severed the costal arches move outward normally and equally.

In the animals in Group I a portion of the intercostal muscles remained normal. These were proximal to the point of section of the nerve. At necropsy the first nerve was found intact in all the experiments and, therefore, the function of the first intercostal muscle had not been interfered with. All the muscles attached to the wall of the chest below the paralyzed muscles and to the head, neck and shoulders above them combined in the emergency to enlarge the thoracic cavity. The action of these muscles alone or combined was sufficient to overcome the tendency toward paradoxic movement when the diaphragm descended. Therefore, the thoracic wall moved outward with inspiration. The costal arch moved outward and the diaphragm descended at the same time.

In the animals in Group IV the diaphragm did not have any muscular opposition either in the abdominal or thoracic wall, and the costal arches moved outward through an apparently normal excursion. The only explanation that seems possible is that the increased pressure on the abdominal contents caused by the diaphragm's contraction forced the arch outward.

Observations already mentioned showed that the outward movement of the costal arch and the wall of the chest whose muscles were intact was bilaterally equal even when half of the diaphragm was paralyzed. This is true after phrenic neurectomy in man as well as in the dog. In the latter the measurements can be taken before killing by overetherization after stripping the costal arch of all superficial structures; the visible movement and the measurements are, then, not confounded and confused by the overlying integument.

In the animals in whom the spinal cord was transected and one phrenic nerve cut the contraction of the hemidiaphragm was not associated with decreased movement of the costal arch on that side. Therefore, the pressure on the abdominal contents must have been distributed equally in all directions. Only such pressure could have caused a paralyzed chest to move outward as if taking active part in inspiration.

I would not be willing to apply all of the results of these observations to man except in a very general way. It might be said, however, that the surgeon who expects to operate on the thoracic cage may proceed without apprehension, regardless of the extent of the operation, if the integrity of the lung is such that there is a wide difference between the patient's vital capacity and his requirements of tidal air.

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THE ULTIMATE PROGNOSIS IN HAY FEVER.*

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Every patient wants to know what are the chances that the treatment of his hay fever in any one year will lead to results which will be permanent, and if not permanent, whether the immediate procedures will modify other treatment in later years. We have found, occasionally, that treatment in one year, or in two years, was followed by relief of hay fever which was apparently permanent. We have several patients who have shown progressive improvement as the years went by, and frequently with treatment which was less and less extensive. But the larger number of patients seem to be quite as sensitive in the following years as they were in the first year and the same prolonged series of from 10 to 15 doses appears necessary. How frequently is a permanent result obtained?

Hay fever has three principal groups, which accord with the different pollen causes. For various reasons, we have been most interested in the late group, in which hay fever depends on ragweed pollen, and the following report is based on it. Only those patients are included who began their treatment in or before the season of 1925 and who have been followed for at least two years. We have

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indicated the results in these terms: The word "cured" is applied only to those patients who have had no hay fever and no treatment for a period of at least two years. The term "greatly improved" is applied to patients who have been essentially free of hay fever, but who may have had some treatment. The other classifications, "improved" and "unimproved" have been also noted.

A total of 410 patients with ragweed hay fever have been traced. The end results show that 26 of these 410 patients (6.3 per cent) have had no further hay fever since the last treatment, which was two years or more ago. Although these cases began treatment in different years, the various first, second and third years, respectively, of their treatment have been considered together, regardless of the particular fiscal year in which the treatment began. Table I shows the gross results, as follows:

TABLE I.—RAGWEED HAY FEVER. GROSS RESULTS ACCORDING TO NUMBER OF SEASONS TREATED.

No. of seasons treated.	"Cured."	Greatly improved.	Improved.	Same.	Total.
1 season	15	44	23	34	116
2 seasons	5	22	11	6	44
3 seasons	2	52	12	17	83
4 seasons	1	27	5	3	36
5 seasons	2	24	9	5	40
6 seasons	0	27	7	4	38
7 seasons	1	14	2	2	19
8 seasons	0	18	1	0	19
9 seasons	0	10	3	2	15
Total	26	238	73	73	410

Figures indicate number of patients.

Of the 116 patients who were treated for one year only, 15 have remained free of hay fever and without further treatment in the meantime. In addition, 44 patients are greatly improved.

Forty-four patients were treated for two years and, of these, 5 are "cured" and 22 are greatly improved. Table I shows similar figures for the results after more years of treatment. This table shows, of course, a diminishing number of patients, in accordance with the increasing number of years, until finally, we see only 15 patients, who have been treated for nine years.

The number and percentage of "cured" cases in this series is extremely small, and it is worth while to analyze them from several points of view.

First, as we have just seen, "cure" does not depend upon the total number of years of treatment; quite on the contrary, about one-half of the total "cures" have occurred among those patients who were treated for only one year, and it is evident that patients who must have treatment for more than five years are rarely "cured." Second, the duration of "cure" in these cases is of impor-

tance in emphasizing the permanency of these results. Thus, 4 patients have had no hay fever for the past seven years, 2 patients are free for six years, 8 for five years, 3 for four years, 5 for three years and 4 for two years; which means that, for the whole series of 26 patients, the average duration of freedom from hay fever is 4.3 years.

Third, the question comes up whether more "cures" were brought about by the particular treatment in one fiscal year than in another, which might indicate that better extracts and better methods of treatment were employed in that particular year.

TABLE II.—LATE HAY FEVER, "CURED" CASES.

(*Clinical Data.*)

Case No.	Patient's initials.	Sex.	Age when first treated.	Age at onset.	Years treated and results.	Skin tests in 1928.	Remarks.
1 . .	A. S.	M.	10	5	1920,‡ 1921,‡ 1922‡	Pos.	
2 . .	C. L. R.	M.	12	10	1923,¶ 1924,¶ 1925¶	Neg.	
3 . .	W. L. B.	M.	15	9	1921,† 1922*	Neg.	
4 . .	L. A. S.	F.	18	17	1922†		
5 . .	H. M.	M.	18	16	1920‡		Double H. F.
6 . .	M. K.	F.	19	13	1923¶	Pos.	
7 . .	L. M.	M.	24	19	1919†	. .	Double H. F.
8 . .	D. R.	F.	26	22	1924¶		
9 . .	F. B. M.	M.	26	19	1921¶		
10 . .	T. H. C.	M.	28	18	1920‡	Neg.	
11 . .	E. S. D.	M.	30	6	1920,¶1921¶		
12 . .	R. P.	M.	32	30	1923¶	. .	Double H. F.
13 . .	E. W.	F.	33	32	1921†		
14 . .	P. L.	M.	34	8	1922‡		
15 . .	W. H.	M.	34	10	1920,* 1921,‡ 1924‡		
16 . .	E. S.	M.	34	15	1922,* 1923,¶ 1924¶	Pos.	
17 . .	E. W.	M.	37	12	1920,‡ 1921,‡ 1922,¶ 1923,¶ 1924¶	Neg.	Old Case§ No. 22
18 . .	R. C.	F.	38	4	1920,† 1921,† 1922†	. .	Double H. F.
19 . .	W. S. P.	M.	39	14	1922¶	Pos.	
20 . .	A. Q.	F.	40	38	1920¶		
21 . .	H. C.	F.	40	30	1922*	Pos.	
22 . .	A. P.	M.	48	6	1920‡		
23 . .	J. S.	M.	48	43	1922†	Neg.	
24 . .	R. A.	F.	52	12	1920,‡ 1921,¶ 1922,¶ 1923,¶ 1924,¶ 1925¶	Neg.	Old Case§ No. 1
25 . .	E. F. B.	F.	53	17	1921,† 1922¶		
26 . .	J. E. B.	F.	54	28	1920,¶ 1921,¶ 1922,‡ 1923‡ 1924¶	. .	Old Case§ No. 4

Although the data are not shown, it can be said that the treatment given in 1920, to new and old patients, has resulted in 5 permanent "cures" among a total of 91 patients, 5.5 per cent, and that in 1922 there were 5 "cures" among 80 new patients, and 9 "cures" among a total of 175 old and new patients treated, 5.1 per cent; figures which are both much higher than the average, which shows only

26 permanent "cures" in a total series of 1442 individual courses of treatment, 1.8 per cent. There is some evidence, therefore, that the treatment in 1920 and in 1922 was more effective in producing permanent results than the same sort of treatment in others years. However, such a thought is hard to correlate with the immediate results, observed at the close of each season, which have shown, as already published,[1] that the years of 1920 and 1922 were a little below the average.

Table II indicates the experiences with each of the 26 "cured" patients. This table shows the age of onset of hay fever and the age at the first year of treatment. The age of onset varies from four to forty-three with an average of 17.4 years, which we have found is close to the average for a large series of 972 patients with ragweed hay fever. There are a few more males than females. The years of treatment have following them small figures which indicate each immediate result, "¶" being perfect. Finally, the lapse of time between the last treatment and the present time can be found by subtraction.

This table and Table II–A, which accompanies it, are worthy of careful study. They show all the factors discussed above, and in addition, they bring out this important observation: that even though the immediate results of treatment be only "†," slight improvement, or even "*," unimproved, a permanent "cure" may eventually follow. These observations show that permanent relief of hay fever is not always and necessarily dependent upon the particular treatment method.

TABLE II–A.—EARLY HAY FEVER, "CURED" CASES.

(*Clinical Data.*)

Case No.	Patient's initials.	Sex.	Age when first treated.	Age at onset.	Years treated and results.	Skin tests in 1928.	Remarks.
1 . .	R. P. S.	M.	12	7	1920‡	Pos.	
2 . .	E. E.	F.	15	10	1923†		
3 . .	H. M.	M.	18	16	1920‡	..	Double H. F.
4 . .	E. P.	F.	19	18	1924,¶ 1925‡	Pos.	
5 . .	M. D.	F.	20	6	1923,† 1924‡		
6 . .	L. M.	M.	24	19	1919†	..	Double H. F.
7 . .	R. P.	M.	32	30	1923¶	..	Double H. F.
8 . .	R. C.	F.	38	4	1920,† 1921¶	..	Double H. F.
9 . .	M. K.	F.	50	43	1920,¶ 1922,¶ 1923¶	Pos.	
10 . .	M. T.	F.	59	33	1925†		

Results indicated by figures under each year as follows:

* Unimproved.
† Slightly improved.
‡ Greatly improved.
¶ Completely relieved.
§ Old cases described in previous article.

On the other hand, the low percentage of permanent results probably does reflect a technique of treatment which in general is less effective than that of other workers. Indeed, the average figure for perfect immediate results, given in the earlier report[1] was 10 per cent whereas Vander Veer's[2] perfect immediate results, as published in 1922, were 23 per cent, and Walker's[3] immediate results, in 1921, were 25 per cent good. The publication of further reports of permanent results will help to settle this question. In this connection, it is very unfortunate that Walker's recent discussion of 100 cured cases[4] did not include a statement as to the size of the total series represented.

That the figures given for the "cure" of late hay fever are not wholly unreasonable is supported by the results in early hay fever and in double hay fever, which shows that of 144 patients with early hay fever (Table II–A) 10 (7 per cent) have been "cured," while of 50 patients with double hay fever, included in the other groups, 4 (8 per cent) have been "cured."

Table II also indicates the results of skin tests done in the spring of 1928. Unfortunately, only 12 of these patients have been so tested, but the skin tests are positive in 6 of the 12, and if this is so, it shows that the clinical "cure" is not necessarily and always accompanied by disappearance of fixed antibodies. One of these 6 patients was a small boy, aged twelve years, who was treated in 1921 with timothy. In the six seasons since that time he has had no further treatment of any kind and yet he has had no hay fever. To-day, however, his test is just as large as it was before treatment. Another patient is a doctor, aged thirty-nine years, treated with ragweed in 1922, but not treated since then. In spite of no treatment, he has had no hay fever in the intervening five years. His skin test is now almost as large as it was at first, and his blood serum is able to transfer the ragweed sensitiveness to the skin of a normal subject. Obviously, he must be sensitive to ragweed, and, obviously, the word "cure" can apply only to the degree of sensitiveness. In this connection, attention is called to the patient with egg poisoning, previously reported,[5] who although able to eat an egg every morning for breakfast, still gives a positive skin test to egg white and still has egg reagin in his blood. Levine and Coca[6] have described 3 patients who have positive skin tests and reagins in their blood, but who have no symptoms at all.

These results in hay fever are distinctly disappointing. They indicate that our prognosis must be guarded always. A fact not brought out by the data, however, is that in a certain number of the cases, it is quite possible to reduce the amount of treatment which is given in each successive year, so that when a patient has had, for example, 15 doses in the first year, his treatment can frequently be reduced to 12, 10, 8 and 6 doses and, finally, down to 3 or less doses in the last years. The exact number of patients in

which this can be done is not known. While such a patient cannot be considered "cured," yet the symptoms are relieved by a procedure which later on requires very little time and effort.

Discussion. From the fact that permanent "cure" does not depend upon the exact method of treatment, and occurs in only about 6 per cent of all the patients, one may properly ask whether the permanent "cure" can really depend upon the treatment itself. We can only point out that in most of the cases the relief of hay fever has dated from the time of the last treatment. Why the degree of clinical sensitiveness should diminish from year to year in some patients and remain constant in others cannot be explained. The fact that clinical sensitiveness can disappear without a change in the skin hypersensitiveness, certainly indicates that the "cure," in these cases at least, does not depend upon a profound change in the entire organism, but must depend, as Levine and Coca[6] have already pointed out, upon a change in the local sensitiveness of the conjunctival and nasal mucous membranes. In general, we may say that "cure" is a clinical rather than a true immunologic phenomenon.

Summary. 1. In a total of 410 patients with ragweed hay fever, relief of symptoms, which appears to be complete and permanent and without further treatment, has occurred in 26 patients, or 6.3 per cent.

2. The relief has persisted for an average duration of 4.6 years.

3. This relief ("cure") does not depend upon the total number of years of treatment, nor does it apparently depend upon a particular technique of treatment.

4. "Cures" among patients with early hay fever occur in 7 per cent, a comparable figure.

5. Inasmuch as skin tests may be positive in the presence of long standing and complete relief, "cure" must be, in most cases, a clinical rather than an immunologic phenomenon.

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A DEPARTURE FROM THE USUAL METHODS IN TREATING OBESITY.

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Obesity, in degrees worthy of comment, has for sometime been appreciated by physicians as a menace to continued health. It has not been so considered by most patients, even when constituting a frankly pathologic condition. Any rational treatment demands intelligent coöperation of patients, and for these reasons, in the past, satisfactory results were not always obtained. Recently, however, since people have become more interested in preventive medicine, from a personal point of view, overweight is being taken more seriously. More patients than formerly are presenting themselves to physicians complaining of obesity alone, and of these a gratifying percentage make the necessary sacrifices for relief and coöperate willingly.

The apparent paradox that some people get fat and others do not on what appears to be equivalent diets has invited much speculation. In a few cases, of course, a lowered metabolic rate and increased sugar tolerance is associated with endocrine disorders. These are outspoken cases of endocrine disease and are rare. In the vast majority of persons no such disorders are demonstrable. One might expect that these people have normally a lower metabolic rate, but we have ample evidence that when calculated by the usual methods, it is within normal limits: (Jones;[1] Preble;[2] Means;[3] Strouse, Wang and Dye;[4] Lauter;[5] Labbé and Stèvenin[6]). In normal persons, combustion is speeded up after protein ingestion due to the specific stimulative effect of certain amino-acids on the oxidative processes of the organism. It has been suggested that in the obese this so-called specific dynamic action of protein is not so marked (Gibbons;[7] Strouse, Wang and Dye[4]). Recently some observers (Wang, Strouse and Saunders;[8] Hagedorn, Holten, Becht;[9] Wang and Strouse[10]) not only postulate a diminished specific dynamic action of protein in the obese but also some abnormality of fat metabolism by which it is spared and thus becomes available for storage. These patients are said to use protein and especially carbohydrate more easily than normal, so much more easily than fat that as long as any protein and carbohydrate is available no fat will be used. If these suggested disorders of metabolism in the obese do exist they are, possibly, dependent upon an endocrine cause.

imbalance varying in some minor degree from the accepted normal. But it is none that is now recognized and, therefore, not a condition which can be treated by any rational endocrine therapy. No person, whatever his endocrine function may be, will gain in weight if his caloric intake balances or is less than his energy output. And, except in those rare cases in which obesity is associated with the true endocrine disorders too widely known to need description here, in which endocrine therapy should be instituted for the endocrinopathy itself, endocrine products should not be thought of in connection with obesity. The treatment should be dietary, and dietary alone.

One hears all sorts of fads and fancies in diet suggested for reducing weight. No special article of food has any merit in this regard. Total calories must be reduced. Folin and Denis[11] tried, apparently with good results, alternate periods of complete fasting and absolute freedom of diet. Most régimes, however, merely state that sufficient protein be given to keep the patient in nitrogen equilibrium and total calories be reduced by a lowered intake of carbohydrate and fat, reducing the caloric intake cautiously and the weight gradually. This is safe, rational, and may frequently be carried through.

If we thought of this problem with the same metabolic insight as used in the dietary treatment of diabetics, could we not with safety be somewhat more radical? Instead of cautiously reducing the diets of the obese to 14 or 15 calories per kilogram with resulting weight losses of 6 to 8 pounds a month, would it not be safe in some cases to give them half as many calories, say 6 to 8 per kilogram, and get a more rapid reduction? It was tried and found satisfactory.

The method used has been to calculate the correct diet for the ideal weight or whatever weight is desired. Different from diabetes, more than enough protein has been given to keep the patient in nitrogen equilibrium, 1 gm. of protein per kilogram, because in the treatment of obesity the specific dynamic action of protein probably was desirable. With a gram of protein per kilogram, enough carbohydrate and fat was calculated to give 25 calories per kilogram, the carbohydrate and fat in such proportion that the ketogenic-antiketogenic ratio was 1½ to 1. Having obtained the figures for protein, fat and carbohydrate, the menu was made up to fit the figures for protein and carbohydrate, and as much of the fat was omitted as could be, while allowing the patient the desired amount of protein.

For example: A woman, married, aged thirty-four years, 64 inches tall, should have an ideal weight of 60 kg. The diet for her ideal weight was calculated with 1 gm. of protein and 25 calories per kilogram and carbohydrate and fat in such proportion that the ketogenic-antiketogenic ratio was 1½ to 1. The figures obtained were:

	Grams.	Calories.
Protein	60	240
Carbohydrate	45	180
Fat	120	1080
		1500

The menu made up and given to this patient contained:

	Grams.	Calories.
Protein	60	240
Carbohydrate	45	180
Fat	29	261
		681

The patient weighed 176 pounds or 80 kg. She was, therefore, getting in this diet 8.5 calories per kilogram. Assuming that she needed, not 25 calories as calculated in her reduction diet, but 30 calories per kilogram to maintain her weight, there was a deficit of 21.5 calories per kilogram. She was, therefore, getting in the diet given 1720 calories per day less than she needed to maintain her weight. If these calories were supplied from her own fat she was using 185 gm. of fat, which is equivalent to 212 gm. of her own fatty tissue (12) each day, 1500 gm. per week. She might be expected to lose, therefore, not 6 to 8, but 12 to 14 pounds a month.

The possibility of the development of acidosis on this diet does not appear to be great. The maximum possible ketogenic-antiketogenic ratio, according to Woodyatt's formulæ, may be estimated by assuming that the entire caloric deficit is supplied by fat alone and that the stored fat metabolizes in the same manner as the fat in the diet. If this assumption is correct the caloric deficit of 1720 is equivalent to 185 gm. of fat. In addition to the 60 gm. of protein and 45 gm. of carbohydrate, the menu supplied 29 gm. of fat. The total amount of fat utilized is, therefore, 214 gm. The glucose equivalent is 101, the fatty acid equivalent 221, a ratio of less than 2.2 to 1. We know that ketogenic-antiketogenic ratios of 2 to 1 are well tolerated, and, under certain circumstances, ratios as high as $3\frac{1}{2}$ to 1 have been used with safety even in diabetic patients. In view of the possibility of a transformation into glucose of some fraction of the endogenous fat metabolized,[13] the actual ratios are probably much lower.

The diet was maintained for ten weeks, during which time the patient lost 42 pounds. She suffered no unpleasant symptoms until the end of this period, when she began to feel tired. The diet was increased until she had gained 4 pounds. The diet was then changed to maintain this weight and she remained so for over one year. The following year she gave birth to her second child, normal in all respects, and since then she has been heavier, but never, over a period of three years, more than 150 pounds.

More radical reduction with higher theoretical ketogenic-antiketogenic ratios have been used in many cases with nothing but the most gratifying results. For example: An unmarried woman, aged forty-six years, $59\frac{1}{2}$ inches tall had an ideal weight of less than 50 kg. The diet for her ideal weight was calculated with 1 gm of protein and but 20 calories per kilogram and carbohydrate and fat

in such proportion that the ketogenic-antiketogenic ratio was 1½ to 1. The figures obtained were:

	Grams.	Calories.
Protein	50	200
Carbohydrate	26	104
Fat	77	693
		997

The menu made up and given to this patient contained:

	Grams.	Calories.
Protein	50	200
Carbohydrate	26	104
Fat	27	243
		547

This patient weighed 178 pounds or 80 kg. She was, therefore, getting in this diet 6.81 calories per kilogram. If we assume that she needed as much as 30 calories per kilogram to maintain her weight, there was a deficit of 23.2 calories per kilogram. She was, therefore, getting in this diet 1856 calories per day less than she needed to maintain her weight. If this was made up from her own fat she was using 199 gm. a day. With the same assumptions as above for the calculation of this menu, we get a glucose equivalent of 78 and a fatty-acid equivalent of 226. This is a ketogenic-antiketogenic ratio of slightly less than 3 to 1.

This diet was maintained for ten weeks, during which time the patient lost 37¼ pounds, and suffered no discomfort or inconvenience. It has now been twelve months since she stopped dieting and she has at no time weighed more than 140 pounds. During this period, no evidence of organic or functional damage has presented itself and there has been no diminution of energy or vitality.

The menu given to this patient and the instructions appended to all menus given out are as follows:

Breakfast: 1 egg, 1 ounce bread.

Lunch: 1 egg, 4 ounces vegetables as listed.

Dinner: 1 cup bouillon (if desired) 3 ounces lean meat (weighed after cooking), 4 ounces vegetables as listed.

Acceptable vegetables: Lettuce, cucumbers, spinach, asparagus, endive, celery, mushrooms, tomatoes, brussels sprouts, watercress, cauliflower, radishes, cabbage, onions—very sparingly.

1. If the bread is eaten as toast, it must be weighed before toasting.
2. Eggs may be taken boiled, poached, or raw.
3. Meat may be boiled, broiled, or roasted.
4. No fried foods may be eaten.
5. No lard or butter may be used in cooking.
6. Vegetables must be prepared without milk, oil, or egg dressing.
7. Water may be taken as desired.

8. Salt, pepper and vinegar (not lemon juice) may be used as desired.

9. *It is just as important* that all this be eaten as that nothing not on the list be taken.

10. Take a level teaspoonful of soda in half glass of water twice each day.

No thought was given to vitamin or salt content of the diet, the menus given being considered satisfactory in these regards for the limited periods of dieting required. The patients were urged to eat preferably the salad vegetables which could be taken raw. With salt, pepper, vinegar, and egg when listed, and mineral oil, many patients developed salad dressings to satisfy the most exacting.

Using this method for metabolic orientation, a number of patients have been kept for weeks on diets containing less than 8 calories per kilogram. This report is based on 111 patients who are either completed cases or have been dieting four weeks. These patients averaged 47.5 per cent overweight. Among them 5 patients were 100 per cent overweight, 11 were 75 to 100 per cent overweight, and 27 were 50 to 75 per cent overweight.

Ninety-eight patients are completed cases. Their data may be summarized as follows:

98 patients in 858 weeks lost a total of 2590 pounds.
Average time on diet, 8.75 weeks.
Average loss per patient, 26.4 pounds.
Average loss per week, 3.02 pounds.

The data for the 111 patients at the end of the first week summarized is:

111 patients lost 714 pounds.
Average loss per patient, 6.43 pounds.

Figures are available for exactly four weeks on 75 patients. This data summarized is:

75 patients lost 1209 pounds in four weeks.
Average loss per patient in four weeks, 16.1 pounds.
Average loss per week, 4.03 pounds.

Forty-seven patients were weighed exactly at the end of eight weeks. This data in summary is:

47 patients lost 1265 pounds.
Average loss per patient, 26.9 pounds.
Average loss per week, 3.36 pounds.

This rapid reduction is satisfactory only if the patient is not damaged by it. All the patients thus treated have at the end of a week felt much better and, at the end of two weeks, were quite enthusiastic. Statements such as "I am sleeping better than for years," are common throughout the entire period of dieting. During the first two to three days there was sometimes headache, dizziness,

weakness, occasionally nausea; but this had passed by the fourth day. A bad taste in the mouth lasted very often for a week, but no longer. All these patients had acetone in the urine at first, sometimes for weeks, but still were enthusiastic in their expressions of well-being.

So far, there have been no disasters or even minor misfortunes. The hemoglobin and red-cell counts have either remained the same or increased, and there has been no acidosis. Eighty-eight of these patients have been followed for six months or more after being thus radically reduced and none have shown a floating kidney, splanchnoptosis, hernia, or, where varicose veins were present, anything but improvement in them.

All the cases were thoroughly examined for contraindications before the treatment was undertaken. No doubt a tuberculous lesion would be a contraindication, but the list of others has been growing smaller as experience increases. Patients with myocardial lesions are supposed to be poor subjects for reduction, and they probably are. Among these patients there were 8 with definite evidence of myocardial damage and many with symptoms, such as dyspnea, swelling of the feet, and palpitation, suggesting minor grades of myocardial insufficiency. These patients were dieted exactly as the others and, with one exception, the results were just as gratifying. The exception was a case shown, six months after dieting, to be complicated by a psychopathic lesion leading to moral turpitude of a criminal nature for which he was convicted and confined.

Adolescents and the elderly are thought to bear reduction cures poorly. There was one twelve-year-old girl in the series, who reduced from 208½ to 164½ pounds—44 pounds—in twenty weeks, with nothing but marked improvement in her physical and mental equipment. Another girl, aged sixteen years, was reduced from 223 to 143 pounds—80 pounds—in twenty weeks and she not only improved mentally and physically but a dysmenorrhea of three years' standing disappeared and has not returned in three years.[12] At the other extreme of life, one patient, aged sixty-seven years, came into the office walking with difficulty. She was having 15 to 18 extrasystoles a minute and her blood pressure was 240 systolic, 110 diastolic. She was reduced from 278 to 182 pounds—96 pounds—in twenty-four weeks, an average of 4 pounds a week. After the first two weeks, her extrasystoles disappeared. Her blood pressure after four weeks dieting was 135 systolic, 80 diastolic, and for the last two years has not been above 150. After four weeks, she began doing housework and marketing with ease and comfort. The age range of this short series, twelve to sixty-seven years, would seem to cast doubt on adolescence and senescence as contraindications to the reducing cure, if sound metabolic principles are followed.

The reaction of the blood pressure to this method of dieting is interesting. If it is normal, it remains so. If it is high, in a gratifying number of cases it comes down. In this series of 111 patients, there were 33 with systolic blood pressures above 150. All but one of them showed a lowered systolic pressure after a period of dieting. In some, this was remarkable. One patient with a systolic reading of 215 at the beginning had 135 after eight weeks dieting. Another came down from 260 to 170. The elderly patient mentioned above, whose systolic pressure of 240 was reduced to 135 in four weeks, was seen later after a period of careless eating during a trip to California, 22 pounds heavier than on discharge. In spite of this weight increase her systolic blood-pressure reading was 150. Among 23 patients who had systolic blood pressures between 150 and 200, there were 16 who attained normal figures. For the entire group of 33 patients, the average systolic blood pressure was 189 at the beginning, and 146 after dieting. This is in accord with the findings of Preble[2] and Terry[15] who reduced their cases much more gradually than was done in this series.

Before dieting, a surprising number of these patients complained bitterly of headaches, which in 9 of them were so severe and so frequent as to suggest migraine. In every one, remarkable relief was obtained. One patient under observation at present who previously had two prostating headaches each week, had one the first and second day of dieting and none since, now six weeks. Another, equally bad, had one headache during two months of dieting and another in the succeeding three months. A dull, heavy feeling in the head, complained of by so many, has been completely relieved in all.

A caution about the development of wrinkles and a drawn expression of the face was given to about the first 25 of these patients. It is now no longer given because it was found unnecessary. Except for an occasional deepening of the nasolabial fold and flabbiness resulting from the removal of a "double chin," no wrinkles developed. These patients looked better and younger because of clearer skin and a more animated expression. These features, in contrast to those often found heretofore on reducing patients, suggest that the drawn expression was due to starvation and not to removal of subcutaneous fat of the face.

Minor skin disorders were frequently relieved. Intertrigo disappeared or became easy to control in every case in which it was found. One case diagnosed epidermophytosis, and another with such annoying pruritus vulvæ that oxyuris infestation was seriously considered, obtained complete relief in three and six weeks respectively. It cannot be stated yet that this relief is permanent, for these patients are still dieting.

With the exception of the patient with the psychopathic trend mentioned above, the mental attitude of these patients has been

excellent. The appreciable weight loss during the first week and the feeling of well-being experienced during the second week, which showed them that a rapid weight loss could be obtained without making them sick or interfering with their usual activities, put them in a cheerful frame of mind. The irritability of starvation was entirely absent, indicating that these patients were not being physiologically starved.

These patients were not selected, all presenting being treated the same way, whether of the alimentary or the so-called endocrine type. No difference was found in the reaction of the two types of cases except possibly in the speed of reduction. The symptom obesity, of the cases of "endocrine obesity," can be treated with success by dietary measures alone. Indeed it appears that other symptoms in these cases of "endocrine obesity" yield to this method of dieting, especially menstrual disorders.[12] In many of these patients the flow was scanty, the period prostrating. Most were relieved. Six of these patients had menstrual disorders of pathologic proportions. All but one were relieved. These will be reported in detail later, but one especially interesting case may be presented briefly here. A woman, unmarried, aged twenty-three years, weighed 150 pounds at the age of eighteen years. Menstruation began when she was fourteen years of age and was normal for eight years. From eighteen until twenty-two years of age she gained 50 pounds. Menses then stopped. The patient presented herself, not having menstruated for eleven months, during which time she had gained 50 pounds. She weighed 259 pounds. She had a marked hypertrichosis of the upper lip, chest, forearms, and legs with a masculine distribution of the crines. During twenty-eight weeks' dieting, with a loss of 86 pounds, she menstruated six times without discomfort.

The diets were begun suddenly. All of the patients complained of hunger during the first day, many during the second, and a few for as long as three days. There were only 4 patients in this series who complained of hunger during the entire period of restricted diet. In 2 of these, there was strong suspicion that they kept tempting themselves by nibbles. Many of the patients expressed contentment with the diet. Others lost their appetites and became indifferent to eating, even when active around the kitchen. For this reason, the ninth instruction given them was found necessary and it was always emphasized. None of the patients developed an aversion to food.

Practically all of these patients suffered from constipation, and in some it was really troublesome. This symptom was met in the usual manner and disappeared with resumption of a more generous diet. Agar and bran were not given because with 6 or 7 ounces of 5 per cent vegetables in the diet, it seemed that the constipation was not caused by a diminution of bulk or too refined foodstuffs

The cause of this constipation has not been determined. Possibly the limited carbohydrate of the diet is a factor.

The weight loss was not regular from week to week. In some weeks it would be double that in others. Over a longer period it averaged closely to the calculated figures, however, and after a week with little or no loss one could reassure the patient that in the next she would make up the deficit. This irregularity is due in large part to variations in water balance. Studies on this factor will be reported in detail in a later paper.

When the patients had reached the desired weight, the diet was changed as suddenly as at the beginning. They were put on a weighed diet calculated to maintain them at their present weight and asked to be just as accurate as with the restricted menu. After one month's observation, any corrections necessary were made and they were dismissed for one month. At the end of the second month they were weighed, told to weigh each week and to eat as they desired and could without gaining, and discharged to report in six months. A number of these patients came back saying they had found they could eat as they wanted without gaining. Enquiry revealed that they were eating by choice, after this period of gustatory discipline, just about the proper food.

All these patients continued to lose, and at an increased rate, for one or more weeks after being put on the more generous diet. That this should happen when the diet was suddenly increased so much—often from 600 to 2000 calories—is interesting. The cause of this has been investigated and will be presented in a subsequent report.

Many patients presented themselves for reduction who, when they found out what was necessary, did not go through with it. Practically all those who were faithful for two weeks went to the end. The need for accuracy was emphasized strongly at the beginning and these patients were handled somewhat more firmly than one would care, perhaps, to deal with all his private patients. None of these patients were put in the hospital, all being private patients seen in the office who prepared and weighed their own food at home. It was tried with dispensary patients but did not succeed, these patients being either unwilling or incapable of giving the necessary coöperation.

Conclusion. 1. The importance of metabolic orientation in the treatment of the obese is emphasized.

2. If sound metabolic principles are followed, obese patients can be kept for weeks on diets containing less than 7 calories per kilogram.

3. One hundred and eleven patients, so treated and here reported, lost weight rapidly with nothing but the most gratifying results. They were not hungry. They were cheerful. Headaches were relieved and elevated systolic blood pressures were reduced. Minor disorders of different kinds showed improvement. A sense of well-

being while on the diet—often as low as 600 calories—was obtained which was in sharp contrast to the irritability and cachexia seen with more generous diets not carefully planned on metabolic principles.

4. The obesity of "endocrine obesity" yields to dietary measures as well as that of the alimentary type. Endocrine products are, therefore, not indicated in the treatment of this symptom of these patients.

5. Most of the menstrual disorders so common in the obese are corrected by proper diet alone.

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CHRONIC PENTOSURIA AND MIGRAINE.

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Since the report of the first case of chronic pentosuria by Salkowski and Jastrowitz[1] in 1892, there appear to have been added to the literature to date 78 cases, including this writer's. (See Table I.) In addition, 11 others have been vouched for by several authors but no clinical or chemical studies were published. Thirty-five of these 79 cases are mainly reports of the chemical findings in the urines

TABLE I.—PENTOSURIA CASES REPORTED TO DATE.

4 cases without any clinical symptoms.	40 cases with clinical symptoms present.			35 cases with chemical study mainly.	11 cases with no details given.	24 questionable cases.	3 cases of chronic pentosuria in diabetics.
	Neurasthenia.		6 with other symptoms.				
	22 without headache.	12 with headache.					
Blumenthal	Salkowski-Jastrowitz	Meyer	Rosenfeld	Scognomiglio	Jolles (4)	Reale (morphin addict)	D'Amato
Bial	Blumenthal	Luzzatto (migraine)	Tintemann	Brat	Dunham	Caporali (3) (morphin taken)	Kaplan
Bendix	Bial (3)	Bial (migraine?)	Blum (2)	Kraft (3)	Laband	Columbini (alimentary type?)	Zlataroff
Koopman	Brat	Klercker (2) (migraine)	Cassirer-Bamberger	Blumenthal	Zaudy	Baszewsky (alimentary type)	
	Adler-Adler	Janeway (2) (migraine)	Levy-Pierson	Bial	Fyffe (3)	Weil (patient seen once)	
	Erben	Vas		Rosenberg	Rosenbloom	Stookey (15) (insufficient) chemistry)	
	Rosenfeld	Schuler		Voorthuysen		Alexander (no chemical details)	
	Weil (2)	Aron (migraine)		Levene-LaForge		Rosenbloom (alimentary type?)	
	Chobola	Adler (migraine)		Zerner-Waltuch (2)			
	Vas	Margolis* (migraine)		Hiller			
	Schuler			Fyffe			
	Cohen			Cammidge-Howard (7)			
	Elliot-Raper			Justin-Mueller			
	Zerner-Waltuch			Wrzesnewski			
	Alexander			Rosenbloom (2)			
	Castellani			Hartogh			
	Koopman (2)			Sohlberg			
	Jones-Nissler	Writer's case*		Jones-Nissler (4)			
				Rabinowitch			
				Levy-Pierson (3)			

with little or no clinical facts. Out of the remaining 44 cases, only 31 have been fully described from the clinical viewpoint. It is thus evident that this important phase of study has been greatly neglected.

In 1903, Bendix[24]—following Salkowski's original idea—concluded that chronic pentosuria is not a disease entity, but is simply an anomaly of metabolism. Owing to this prevailing opinion that the symptoms, when present, bear no relation to the accompanying pentosuria, most authors have paid scant attention to the clinical features of their cases. Some are dismissed briefly with "no symptoms," others with "patient is well except for neuralgias or neurasthenia." Very probably some vagotonic signs or intermittent symptoms such as attacks of migraine and urticaria may have been overlooked in some cases because of this attitude. In recent years, few serious attempts have been made to study chronic pentosuria from the clinical aspect. The writer, therefore, proposes to review the subject briefly, add an additional case with a clinical report, and then attempt to classify chronic pentosuria with a group of better known diseases.

Classification. Usually, three types of pentosuria are mentioned: (1) Alimentary pentosuria; (2) chronic pentosuria; (3) pentosuria associated with diabetes mellitus.

Alimentary pentosurias occur more frequently and resemble alimentary glycosuria, that is, by feeding a normal man some pentose, for example l-arabinose, one soon reaches a point above the normal tolerance for that particular sugar (0.5 gm., Ebstein[2]), and l-arabinose appears in the urine. However, this pentosuria is only a temporary one, and soon disappears when the ingestion of the pentose is stopped. Thus, in 1906, Johnstone[32] found pentosuria in 17 out 18 individuals who drank one and a half liters of apple juice. In this type, optically active pentoses (l-arabinose and l-xylose) are usually found in the urine.

On the other hand, in the chronic type, the pentosuria is present for months and years and is not markedly affected by changes in diet. The chemical findings in the urines of this type have not been uniform. Until 1912, the majority of authors reported the finding of optically inactive arabinose, as was originally reported in 1900 by Carl Neuberg.[25] Since 1912, however, optically active pentose, probably d-xyloketose, has usually been reported. As pointed out by Levene and LaForge,[49] Zerner and Waltuch,[47] some of the cases reported as excreting inactive pentose were probably passing optically active pentose, but owing to the small quantity present in the urines, the rotation was so slight as to be overlooked. But at present this explanation does not appear likely in the finding of i-arabinose in some cases (Neuberg, Aron[48]). Therefore, Neuberg[26] and Garrod[61] both suggest the possibility of the existence of several kinds of chronic pentosuria—differing in the pentose found in the

urine. For the present, however, we must classify all chronic pentosurias under one group, as the clinical aspects appear to be the same in all.

As to the third variety, pentosuria present in diabetes mellitus, the writer doubts the advisability of classifying this under a separate group as it may eventually be shown to belong to either of the above two types. The frequency of this combination is still not definitely determined. In 1895, Külz and Vogel[6] found 64 "definite pentosurias" in 80 cases of moderate to severe diabetes mellitus. Similar findings are reported by Pedrazzini[22] and von Alfthan.[41] In 1908, Voit[41] found pentose in 12 out of 14 diabetic urines. On the other hand, Salkowski, Bendix, Kraft, Koopman, and others failed to find any pentose in diabetic urines. Voit himself admitted the difficulty of separating chemically small amounts of pentose from glucose when both are present in the same urine. These conflicting reports, therefore, throw considerable doubt on the subject. On the other hand, we have the individual case reports of chronic pentosuria in diabetics by D'Amato,[21] Kaplan,[34] and Zlataroff.[51] As will be seen later, pentosuria and diabetes mellitus are distinct metabolic entities, and it, therefore, seems best to separate the two diseases.

Frequency. In this study, we are dealing with the second type—chronic pentosuria. Jolles found only 4 pentosurias in 3000 urines and Vas[40] found 2 in over 2000 urines examined. Adler[59] found only 2 pentosurias in 7726 urines, and Koopman[65] found 3 in 4500 urines. Cammidge[65] did not find any in 4500 urines. It would, therefore, seem that chronic pentosuria is extremely rare. However, in 1920, Cammidge[57] reported 7 cases. In 1902, Blumenthal[8] pointed out that 9 cases of pentosuria were reported from the first Berlin clinic alone, and he, therefore, concluded that it could not be so very rare. Stookey[42] claims to have found in a period of two years 15 cases of pentosuria which were not of the alimentary type. Recently, Jones and Sussman[72] pointed out that some of the 52 cases of renal glycosuria lately reported are possibly pentosurias. Chronic pentosuria is without question uncommon, but is probably more common than would appear from the above statistics.

Etiology. A definite cause of chronic pentosuria has not been determined to date. However, the following etiologic factors have been noted:

1. *Heredity.* This factor is indeed very striking and is shown by the frequent occurrence of chronic pentosuria in the same family and the same race. Thus, 24 or about one-third of all the cases reported to date occurred in nine families. These figures are all the more striking when one considers that, in most of the reported cases, there seem to have been no attempts made to examine the urines of the members of the patient's immediate family. Pentosuria occurring in father and son is reported by Cammidge and Howard.[57] Twenty-seven cases, including mine, are reported as

members of the Jewish race, two are Greeks, two English, and in the rest (forty-eight) no mention of race is made. Thus, the Jewish race seems particularly liable to this disease. Unquestionably, we are dealing here with a marked hereditary factor. However, no case of pentosuria observed from birth has been reported to date. The youngest case on record passed a normal urine at the age of twenty-two months and developed pentosuria later on. There are also several cases of an acquired chronic pentosuria on record. This subject will be discussed in greater detail below.

2. *Sex.* At present the males are greatly in the majority. In 1923 Garrod[61] found 33 males out of 44 cases, that is, a proportion of three to one. The writer found 48 males and 25 females (including my case), that is, a ratio of less than two to one. It must be remembered, however, that many pentosurias were discovered at the examinations for life insurance, and undoubtedly more males presented themselves for such examinations. As more cases have been reported, the majority of the males has been reduced, and it would, therefore, seem advisable not to overemphasize this finding at the present time.

3. *Miscellaneous.* Age may play a minor etiologic rôle as 77 per cent of the cases are reported in patients between fifteen and fifty years of age. However, several children are reported between eighteen months and fifteen years and several adults between fifty and seventy-five years of age. Many patients hold executive positions where a great deal of mental strain is present. Klercker[28] stressed this as of possible etiologic significance.

4. *Its Relation to a Disturbance of the Carbohydrate Metabolism.* Some authors maintain that pentosuria is related to diabetes mellitus and they point to the frequent finding of diabetes in the family history of the pentosuric. But both diseases occur frequently in Jews, and it is not unusual to obtain a positive history of diabetes in Jewish families. Many pentosurics were found to have transient glycosurias as well. However, the unstable autonomic nervous system apparently indicated by many of the case reports may account for these temporary glycosurias. No diabetic trend has been noted in a pentosuric to date, although some cases have been followed from ten to twenty-two years. Sugar-tolerance tests performed on pentosurics with various sugars (glucose, lactose, fructose, arabinose, and xylose) have been well within the normal limits. Feeding experiments with galactose have been in the main negative except in a few cases where the increase in the pentosuria was small. However, most of these experiments were conducted upon patients who were reported as excreting i-arabinose. It may be that pentosurics excreting d-xyloketose may show quite different reactions to the administration of some of these sugars. Variations in the amounts of carbohydrates in the diet have failed to show consider-

able changes in the pentosuria. Insulin therapy had no effect on the pentosuria in 3 cases (Rabinowitz,[67] Levy and Pierson,[68] and the writer's case). We can, therefore, conclude that chronic pentosuria is distinct from diabetes mellitus, and does not appear to be related to a disorder of the carbohydrate metabolism.

5. *Its Relation to a Disturbance of the Protein Metabolism.* Several writers have suggested that pentosuria is in some way related to a disturbance in the protein metabolism. Klercker[27] found that the hourly excretion curve of nitrogen in the urine ran parallel to the hourly excretion curve of pentose in the urine when his patient was on various diets (fasting, mixed, low carbohydrate, and milk diets). As he found no change in the amount of pentose excreted when his patient was on a high-protein diet, he pointed out that his above findings simply showed the connection betwen the general and the pentose metabolism. Janeway[36] reported an increase in the urinary pentose when the patient was placed on a diet rich in purins. Cammidge and Howard[57] found a diminution in the urinary pentose (0.5 gm. in twenty-four hours) when the patient was placed on a low-protein diet. The urinary pentose, however, slowly rose to a higher level (3.2 gm.) when a high-protein diet was given. On the other hand, most observers have failed to find an increase in the urinary pentose with large amounts of purines or proteins in the diets. This would seem to indicate that the pentose of the urine is not derived from the pentose of the nucleotides. This conclusion is further strengthened by the fact that the pentose of the nucleotides is d-ribose, while that found in the pentosurias is either i-arabinose (Neuberg) or d-xyloketose (Levene-LaForge, Zerner-Waltuch), neither of which stands in any particularly close relation to d-ribose. In addition, there remain two other serious objections: (1) The other breakdown products of the nucleic-acid metabolism (uric acid, etc.) are not markedly increased in the urines of the pentosuric; and (2) these patients who lose from 3 to 7 gm. of pentose a day should show greater nutritional disturbances, as the total pentose content of the human organs is estimated to be about 10 gm.[16,24] Garrod in his admirable review of this subject concludes that pentosuria is an anomaly of the intermediary metabolism, that the pentose is probably derived from the proteins, and that glucosamine is its most likely parent substance. In 1922, Greenwald[59] concluded from the chemical evidence that pentosuria may be an anomaly of the metabolism of one or more of the amino-acids such as leucin, normal α-amino-caproic acid, glutamic acid, lysine, or ornithine. While this appears to be the most likely viewpoint at present, it must be remembered that only two observers have noted an increase in the urinary pentose with high-protein diets, while many others found no change in the pentosuria. We are, therefore, in great need of additional chemical studies.

Case Report.—Before discussing the symptomatology we shall first describe the following case:

Unmarried female, Jewess, aged thirty-nine years, office executive.

Complaint. Headaches for twenty-five years. "Diabetes" for nine years.

Family History. Father and mother had periodic headaches. One sister, who also has migraine, did not show any pentose in the urine on a single examination. Another sister and a brother (who do not have migraine) failed to show pentose in their urines (single examinations). Father died of angina pectoris. Maternal grandmother was treated for several years as a mild diabetic.

Past History. She has had no serious illnesses. Until sixteen years of age, she had frequent attacks of "hives after eating fish, strawberries, or tomatoes." From childhood to the age of thirty-three years (1921) she had attacks of "frost-bitten" fingers and toes almost every winter—her fingers and toes would swell, get blue, and become painful. Applications of snow helped this condition. Her father, who was a physician, noted a persistent bradycardia since childhood. Menstruation began at fourteen. The flow was normal until about 1919 when it became irregular, and increased in amount and duration. Lower backaches also set in about this time. In 1921, a supravaginal hysterectomy (right ovary retained) was performed and multiple fibromyomata of the uterus were found at the operation. Since then she has had amenorrhea, flushes, cold sweats at times, and a gradual increase in weight. Her headaches have been worse since this operation. There have been no gastrointestinal or genito-urinary symptoms as a rule except during a migraine attack. Occasionally a sudden and forceful vomiting of a recently ingested meal would take place without any preceding nausea and without any apparent cause. Similar attacks of nausea, abdominal cramps, and diarrhea, occurred occasionally. In 1927, her tonsils were removed on account of frequent sore throats and colds.

Present Illness. This began about twenty-four years ago, and it came on about two and half years after the onset of menstruation. The attacks always occurred at the time of the menses, but in addition frequently between the periods. An attack is described as follows: The headache comes on first, at times suddenly, is frequently followed by nausea, and less often by vomiting. "Extreme nervous exhaustion" follows an attack and sometimes lasts for several days. The pain is described as "sharp, pounding, pressing and pulling." Its distribution is unilateral as a rule (the left side more frequently) and occurs over the supraorbital, temporal, and infraorbital regions, cheek, upper jaw and teeth, ear, and occipital region. An attack often comes on at night and she wakes up with a headache. Not infrequently, she has fainted away for several minutes with a complete loss of consciousness. These attacks while occurring periodically do not come in definite cycles, that is, they may occur every week or once in two or three or four weeks. Between attacks, she has "a lucid period"—she feels relatively, but not entirely, well. For many years she has tired very easily, and is frequently mentally depressed. During attacks she becomes quite nervous, very irritable, and feels chilly. Pressure on the temples, hot applications to the head, rest in bed, and sedatives have relieved her to a certain extent. During vacation periods, the attacks are less frequent and not so intense. In 1918, she was rejected for army service on account of having "sugar" in her urine. Ever since, she has been treated as a "mild diabetic" but strictly low-carbohydrate diets have failed to eliminate the "glycosuria." At no time did she have any diabetic symptoms. From November, 1926, to January, 1927, she was under the care of a physician who placed her on a low-carbohydrate diet and daily injections

of insulin. This had no affect on the glycosuria. On January 5, 1927, he performed a sugar-tolerance test, the result of which is here given with his kind permission. (See Table II.) Since these results showed a normal tolerance for glucose, and at the same time there was present sugar in the urine, the physician believed that he was dealing with a case of renal glycosuria. In April and May, 1927, the headaches occurred almost daily and were quite severe. She also complained of "hot flushes, cold sweats, and no energy" at the first visit to my office.

Physical Examination. (Positive findings.) Height 153 cm. Weight 63 kg. Broad type. Moderately obese with adiposity mainly about hips, thighs, and abdomen. Hands small, cold and slightly cyanotic. Feet small. Skin dry. A red flush present over manubrium and face at times. Pupils miotic, react to light and in accommodation. Teeth short, broad, and somewhat crowded. Thyroid not enlarged. *Heart:* pulse rate, 48 to 56 per minute. Blood pressure, 140 systolic and 88 diastolic. Short systolic murmur over the precordium. Tendon reflexes present and active. During a severe migraine attack, the patient showed these additional findings: Patient in bed, shivering, complaining bitterly of headache, nausea, and cold sweats. Face pale, clammy and cold. Hands cold and clammy. Pupils miotic. Pulse, 40 to 44. Frequent twitchings of eyelids. Temperature 35.1° to 35.2° C. by mouth.

Laboratory Findings: Basal metabolism tests— −12 per cent and −15 per cent, May 7, 1927 and March 4, 1928.

TABLE II.—SUGAR-TOLERANCE TEST.

Time. A.M.	Blood sugar, per cent.	Urine. Volume cc.	Specific gravity.	Glucose per cent.	Glucose gm.	Remarks.
9.28	.....	110	1.024	0.15	0.17	Fasting.
9.39	0.096	...	....	....	....	Fasting.
9.44	.....	...	....	....	....	100 gm. glucose by mouth.
10.07	0.105					
10.10	.....	38	1.027	0.19	0.07	
10.40	0.108					
10.44	.....	80	1.008	0.22	0.18	
11.46	0.072					
11.50	.....	430	1.003	0	0	

Roentgen ray of the sella turcica—reported by Dr. M. Pomeranz (May 7, 1927): There is a slight enlargement of the sella turcica. The floor of the middle cranial fossa is thinned but not destroyed. There is no erosion or displacement of the clinoid processes.

Chemical examination of the blood—reported by Dr. A. Bernhard (May 4, 1928).

Urea nitrogen: 10.0 mg. per 100 cc.; creatinin: 0.5 mg. per 100 cc.; uric acid: 2.4 mg. per 100 cc.; sugar: 105 mg. per 100 cc.; CO_2-combining power: 55.7 volumes per cent per 100 cc.

Urine Examinations. (From May 9, 1927 to April, 1928.) Specific gravity, 1.002 to 1.036. Albumin, faint trace occasionally. Benedict's test (qualitative), positive—quantitative tests showed from 0.13 per cent to 2.2 per cent. Repeated fermentation tests, negative. No acetone or diacetic acid. Frequent microscopic examinations revealed no abnormalities. During the first week of July, pentosuria was suspected and a Bial's test gave a positive reaction. A sample was submitted on July 8, 1927, to Dr. A. Bernhard, who reported the following:

Bial's test, positive—checked by spectroscopic examination.

Fermentation test, negative.

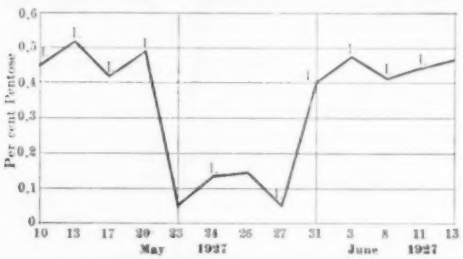
Phenylhydrazine test gave pentosazone crystals with melting point at 156° C.

On September 8, 1927, another sample showed the same finding, except that the melting point was at 159° C. Dr. Bernhard's conclusion was: "The reducing substance in these urines is pentose."

A larger quantity of urine was later submitted to Dr. Isidor Greenwald, who reported as follows:

"A mixed urine was received on October 6. It contained 1.13 per cent nitrogen and its reducing action measured by Sumner's method* or by Benedict's method† was approximately equal to that of a 0.5 per cent glucose solution. In a 2-dm. tube, the rotation was +0.06°. From this, there was obtained a concentrated solution having a specific rotation of approximately +22°. The reducing action of this solution was not appreciably affected by treatment with bromin. The phenylosazone obtained from the urine melted at 157–8°. When 0.2 gm. were dissolved in a mixture of 4 cc. of pyridin and 6 cc. methylalcohol, the rotation in a 1-dm. tube was +0.25°, after twenty-four hours +0.60°. When recrystallized with an equal amount of l-xylosazone the osazone obtained melted at 200–2°. This elevation of the melting point is characteristic of d-xylosazone and, therefore, the sugar appears to be d-xyloketose, which was also found in the cases reported by Levene and LaForge, Zerner and Waltuch, and Hiller."

CHART I.—EFFECT OF MILK INJECTIONS ON PENTOSURIA.



I, Indicates dates injections given.

Clinical and Chemical Studies. The patient was at first placed on a low-carbohydrate diet, and ovarian (1 gm.), thyroid (0.05 gm.) and pituitary (0.033 gm.) glands were taken by mouth daily. Injections of an ampule of whole ovary hypodermatically and of milk (½ cc. first injection, all the rest 1 cc.) intradermally were given twice weekly. These injections were given on May 10, 13, 17, 20, 24, 27, 31 and June 3, 8, and 11. No medication was taken by mouth between May 20 and 25. The first three milk injections gave the greatest local reactions, the fourth a moderate one, and the rest slight ones. Between May 22 and June 3, the patient was free from headaches, had more energy, and felt "exceptionally well." During this period, her pulse rate rose to 68 and 70 per minute—the usual range being between 48 and 56 as observed over a period of twelve months. Chart I shows the marked drop in the output of the urinary pentose, which occurred apparently from May 23 to 27 inclusive. All urine specimens (A.M. and P.M.) examined between

* J. Biol. Chem., 1925, **65**, 395.
† J. Biol., Chem., 1926, **68**, 764.

May 10 and 23 and May 30 and June 13 contained between 0.4 per cent and 0.5 per cent of pentose. On May 23, a specimen collected at 11 P.M. (four hours after dinner) with a specific gravity of 1.010 failed to reduce Benedict's solution (1 cc. urine to 5 cc. Benedict's solution). A similar occurrence took place on May 27 when the morning specimen (sp. gr. 1.020) collected before breakfast also gave a negative Benedict's test. Between these two dates, an A.M. specimen (sp. gr. 1.016) on May 24 and a P.M. specimen (sp. gr. 1.026) on May 24 failed to reduce 5 cc. of Benedict's solution when ½ cc. of the urines were used, but there was a reduction with 1 cc. From May 31, 1927, to April, 1928, all the urine specimens examined (over 200) gave a positive Benedict's test (with ½ cc. of urine). We have therefore the following interesting coincidence: The first 4 intradermal injections of milk which gave the greatest local reactions are followed by a marked clinical improvement lasting for two weeks, and during this time there is a marked diminution of the pentosuria, lasting apparently for five days.

CHART II.—EFFECT OF PEPTONE INJECTION ON PENTOSURIA.

Method of collection of urines: (This applies to Chart I, II and III up to January 20.) Patient voided at 7 P.M., ate dinner before 8 P.M., collected specimen at 11 P.M., then collected specimen at 7 A.M. before breakfast. Chart I shows single specimens on given dates. Chart II illustrates average concentrations of P.M. and A.M. specimens.

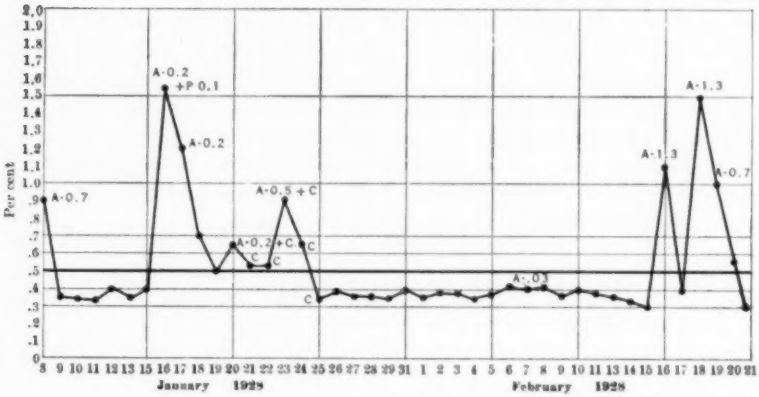
Attempts were made later on to duplicate the above findings. However, no clinical or urinary changes took place with additional injections of milk, with endocrine therapy alone, or with a combination of the two. At the same time, we did not obtain the previous marked local reactions. Later on 10 injections of a 5 per cent peptone solution (Armour) were given intravenously in the following doses: 0.3 cc., 0.6 cc., 0.9 cc., 1 cc., 1 cc., 1.2 cc., 1.3 cc., 1.6 cc., 1.8 cc., and 1.8 cc. (See Chart II.) Here again the clinical symptoms and the pentosuria remained unchanged, and at the same time there were no apparent general reactions.

By this time, it was noted that an increase of over 0.6 per cent of pentose occurred on some days. Thus Chart II shows this increase on November 25, 29, and December 2. Chart III shows similar

increases on January 23 (0.9 per cent) and February 16 (1.1 per cent). These and many other similar observations were made and on each occasion a severe migraine headache was present. At first this increase was thought to be due mainly to the headache, but later on the writer noted that amidopyrine in the presence or absence

CHART III.—EFFECT OF AMIDOPYRINE ON PENTOSURIA.

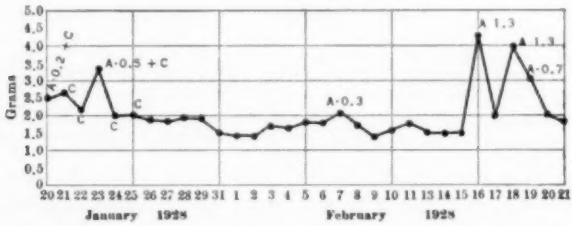
(In terms of per cent of pentose.)



10.3 per cent pentose for February 21.

CHART IV.—EFFECT OF AMIDOPYRINE ON PENTOSURIA.

(In terms of twelve-hour output of pentose in grams.)



A indicates amidopyrine taken in grams. *P* indicates pantopon taken in grams. *C* indicates codein taken in doses of 0.02 to 0.03 gm.

Method of collection of urines: (This applies to Chart III after January 20 and to Chart IV.) Patient voided at 7 P.M., ate dinner before 8 P.M., saved all specimens to 11 P.M. in one container, then saved all specimens to 7 A.M. in another container. Incomplete specimens on January 14, 30 and February 12.

of a severe headache raised the output of the urinary pentose. Thus, on January 23, 0.5 gm. of amidopyrine and on February 16, 1.3 gm. were taken by mouth to combat a severe migraine attack on each occasion. Chart IV shows the total output of urinary pentose in grams over a period of twelve hours (from 7 P.M. to 7 A.M.). Charts III and IV illustrate the following findings:

1. The curves of the percentage and of the twelve-hour output of urinary pentose run closely parallel to one another.

2. The percentage and the total twelve-hour output of pentose are remarkably constant except when amidopyrine is taken.

To make certain that the increase was due to the amidopyrine an equal amount (1.3 gm.) was again given on February 18. On this day, the patient felt relatively better than on February 16, but there was a mild headache present. A sharp rise (4 gm.) in the pentose output again took place (see Chart IV). On February 19, with no headache present, the patient took 0.7 gm. of amidopyrine and the level of the pentose excretion was higher than on the days without the intake of amidopyrine. Thus a little over 1 gm. of amidopyrine is apparently capable of increasing the usual total twelve-hour output of pentose by over 2 gm., or more than 100 per cent of the usual amount.

Blumenthal and others have drawn our attention to the increase of combined glycuronates in the urines of patients who are taking morphin, antipyrin, pyramidon, chloral, camphor, etc. The writer, therefore, gave 1.3 gm. of amidopyrine to 11 individuals and obtained the following results:

1. Five apparently normal persons (without migraine) were given 1.3 gm. from one to three days, and twelve-hour urine specimens collected daily. All specimens were negative to Benedict's and Bial's tests, before, during and after taking the medication.

2. Five patients with migraine gave similar negative results.

3. One patient with acromegaly took 1.3 gm. amidopyrine daily for two weeks. His urine was uniformly negative for reducing substances.

To determine the nature of the pentose excreted during the period of medication, the specimens were submitted to Dr. Isidor Greenwald who very kindly sent me the following report:

"The urines obtained from the evening of February 15 to the morning of February 22 were examined. Nitrogen was determined by Kjehldahl, sugar by the Benedict copper and the Sumner methods. The evening specimens of February 16, 18 and 19, and the morning specimens of February 17 and 19 contained much more sugar than did the corresponding specimens on other days. That this increase was actually pentose was shown by the following experiment. Such volumes of each specimens as contained, using the results obtained by Benedict's copper method, pentose equivalent in reducing action to 100 mg. of glucose were measured into a series of tubes. After diluting all to the same volume, 31 cc., 5 cc. of a clear, filtered 10 per cent solution of phenylhydrazine hydrochlorid and 7.5 cc. of 10 per cent sodium acetate were added to each tube. After mixing the contents of each tube, these were then immersed in a boiling water bath for two hours and were then allowed to cool overnight. The osazones were then filtered out, washed, dried, and weighed. The amounts obtained are indicated in Table III. It is evident that the yield of osazone from the same amount of reducing substance is rather greater in those urines containing the greater concentrations of reducing substance than it is in the others. This

is to be expected, for the same 100 mg. of "glucose equivalent" is accompanied by a smaller amount of other substances (urea, and so forth). That the osazone obtained from these specimens was actually d-xylosazone was shown by the melting-point, 155° to 157°, and the rotation. The osazones obtained from the evening specimens of February 16 and 18 and the morning specimen of February 17 were extracted with chloroform to remove a little tar. After drying, 0.20 gm. were dissolved in a mixture of 6 cc. methyl alcohol and 4 cc. pyridin. In a 1-dm. tube, the rotation was +0.20°. After twenty-four hours, it was +0.40°. When mixed with an equal quantity of l-xylosazone and recrystallized, the melting-point was raised to 200–2°."

We may, therefore, conclude that amidopyrine markedly increases the output of the urinary pentose although the headache and the nervous symptoms when present may account for some of the increase. The source of this increased pentose content lies unquestionably in the general metabolism as the total body content of about 10 gm. of pentose is insufficient to account for the great daily loss. Dr. Greenwald pointed out to the writer that this effect of amidopyrine may be similar to the effect of phlorhizin on glucose excretion or else to the quite different effect of cinchophen on the elimination of uric acid. It is interesting to note that with the possible exception of pantopon, amidopyrine gave the patient the greatest relief, whereas the barbital derivatives and Cannabis Indica failed to control the severe migraine attacks and also had no effect on the pentosuria.

TABLE III.—SUGAR AND OSAZONE DETERMINATIONS IN MORNING AND AFTERNOON SPECIMENS OF URINE.

P.M. Specimens.
(From 7 P.M. to 11 P.M., approximately.)

Date February.	Volume, cc.	Nitrogen, gm.	Sugar. Benedict, gm.	Sugar. Sumner, gm.	Osazone from 100 mg. sugar, gm.
15	265	1.25	0.86	0.70	0.060
16	190	1.48	2.21	2.11	0.090
17	190	1.60	0.92	1.05	0.106
18	160	2.29	3.16	2.82	0.091
19	90	1.17	1.49	1.17	0.084
20	140	1.81	0.99	0.92	0.077
21	163	1.55	0.85	0.87	0.090

A.M. Specimens.
(From 11 P.M. to 8 A.M. approximately.)

16	385	2.51	1.23	1.14	0.069
17	195	2.36	2.64	2.76	0.095
18	300	3.85	2.34	1.87	0.068
19	100	1.35	2.00	1.86	0.092
20	220	3.45	2.78	2.50	0.083
21	235	3.28	1.30	1.38	0.076
22	600	3.15	1.24	1.42	0.078 used 38 cc. for osazone

Symptomatology. As previously stated the present prevailing opinion assumes that the chronic pentosuria by itself does not produce any symptoms. Thus Bendix,[23] Bial,[13] and others maintain that the nervous and other symptoms usually present are merely accidental findings, and therefore chronic pentosuria is not a clinical entity but simply a harmless anomaly. However, almost from the beginning a few observers disagreed with this conception. Meyer[14] believed that the high-protein diet, the nervous and other symptoms and the pentosuria were related in some way. Klercker[27] and Schüler[44] maintained that the cause of the pentosuria was linked up with the neurasthenic habitus found in most cases of pentosuria. Aron[48] and Bial[13] on the other hand argued against this conception because when the nervous symptoms disappeared the pentosuria was still present. Alexander[54] believed that the gastrointestinal upsets as well as the nervous symptoms were responsible for the pentosuria. In reviewing the literature, the writer noted the following symptoms mentioned frequently:

1. *Neurasthenia.* This clinical catch-all includes nervousness, fatigue, neuralgia, backaches, headaches, sweats, globus hystericus, emotional upsets, irritability, cold extremities, fleeting pains and aches, dizziness, chilly feeling, palpitation, spastic constipation, spastic colitis, and bradycardia. "Neurasthenia" is found in 77 per cent of the pentosurics who were described clinically to some extent, and frequently a positive family history of neurasthenia is also given.

2. *Headaches.* Twelve (or 27 per cent) of the cases (44) with some clinical study had headaches as a predominating symptom. (See Table I.) Eight of these were of the migraine type, and one other mentioned very briefly by Bial[13] is probably migraine. In this latter case, the patient who is of nervous stock had light unconscious spells in addition to his headaches. The other 3 cases with headache are difficult to classify. Chobola[69] reports that his patient's mother had migraine. Possibly other cases of pentosuria had occasional migraine attacks which were either overlooked or considered unimportant by the author reporting the case. In any event, we have a rather frequent association of two diseases, one common, the other uncommon, and both possessing a marked hereditary factor; that is, in migraine about 46 per cent of the cases have a positive family history for migraine[71] and in pentosuria 30 per cent have a positive family history for pentosuria. Migraine may occur so frequently as to make this finding an accidental combination. On the other hand, with the frequency of both diseases still not definitely determined, this common association may well point to a close clinical relationship between the two.

3. *Possible Allergic Manifestations.* As migraine is being currently regarded by some authors as a member of a group of allergic diseases, the following cases may be, therefore, of some importance:

(*a*) In Columbini's[11] case, a healthy farmer, aged fifty years, who had been mostly on a vegetable diet for some time, developed a general weakness, and then a widespread itching eruption (Xanthoma diabeticorum). At the height of the disease (one month after its onset) the patient's diet was changed to meat and milk, and he was given 10 to 15 drops of Fowler's solution twice daily. After three months the rash and the pentosuria were no longer present. Unfortunately, Columbini did not make clear how long the pentosuria continued after the change in diet, and this case may possibly be of the alimentary type.

(*b*) In Alexander's[54] case, his patient, aged eighteen months, had intestinal symptoms and pentosuria only when milk was taken by mouth. When milk was removed from the diet the symptoms and the pentosuria disappeared. Infections caused a reappearance of the pentosuria. After three years of intermittent pentosuria, the pentosuria became chronic and lasted for about four years despite all treatment.

(*c*) Meyer[14] found a 50 per cent reduction in the pentosuria when his patient's symptoms (headache, dizziness, loss of weight, and so forth) improved on a moderate carbohydrate diet plus 2 liters of milk a day. After several months, a psychical shock brought back the symptoms and the urinary pentose rose to its former higher level.

(*d*) In Koopman's[65] case, his tuberculous patient had periodic attacks of sharp abdominal cramps which were accompanied by an irregular pulse. These attacks lasted for a short time only. A previous blood smear showed a "few eosinophils." On seven separate examinations, the blood smears made one-quarter to one and a half hours after the attacks showed a pronounced eosinophilia "up to 42 per cent." He concluded that his patient had an "urticaria intestinalis." At present, some authors consider eosinophilia as a positive sign of allergy.

(*e*) Weil's third patient[39] with pentosuria, a pregnant woman, aged twenty-three years, had normal urines on repeated examinations during her pregnancy. From birth to the weaning of the baby (nine months) a lactosuria was present. All along, Weil had not been able to find any pentose, but several weeks after the baby was weaned, the patient's urine contained pentose. Henceforth, a chronic pentosuria set in. Another case of pentosuria in a lactating woman, who also had furunculosis, is reported by Sohlberg.[64] Alexander[54] mentions a case of pentosuria that set in the last few months of a pregnancy where a marked constipation was also present. However, he does not give any chemical details. The intimate clinical connection between pregnancy and the allergic diseases are well known, and it is perhaps important to note that in Weil's case, a chronic pentosuria set in for the first time after a pregnancy and lactation.

The first 3 cases (Columbini, Alexander, and Meyer) may possibly point to the presence of an allergic factor in the diet.

4. *Possible vagotonic cases* (other than those with headaches):

(*a*) In Erben's[35] case, a man aged twenty-one years, there was present a bradycardia (52 to 64), anospasms, irregular bowel movements, "strong" sweats frequently, and fatigue.

(*b*) Alexander[54] described his patient as vagotonic. The boy was nervous, easily aroused, stammered, had constipation and diarrhea. On examination, he found a spastic colon.

(*c*) Spastic and mucous colitis also occurred in 2 young patients described by Blum.[31] One also complained of being frequently tired.

(*d*) Spastic constipation occurred in Tintemann's[30] case.

(*e*) Jones and Nissler[66] found the following symptoms in their patient, a girl aged fourteen years: cyanotic, swollen hands and feet, gastric symptoms, and extreme self-consciousness. They concluded that these symptoms were probably due to an unstable autonomic nervous system. It is interesting to note that my patient also had similar disturbances (cyanotic swollen hands and feet for many years).

5. *Miscellaneous cases.*

(*a*) Cassirer and Bamberger[38] report a case of chronic pentosuria with bilateral neuritis of both femoral nerves. This patient had been rejected for life insurance eighteen years before the discovery of the pentosuria on account of having sugar in his urine. During the past year, he drank a lot of alcohol—"mostly beer, a little wine, and whisky." The patient then temporarily developed bilateral paralyses, involving the quadriceps cruris of both thighs, loss of knee-jerks, tenderness over the femoral nerves, and some sensory disturbances. The authors point out that this is not the usual type of palsies following alcoholic neuritis, but has been noted occasionally in cases of diabetes mellitus and "gouty diathesis." They, therefore, conclude that the coincidental appearance of the two rare symptom complexes may show an intimate connection between the two.

(*b*) Chobola's[69] patient, a boy aged fourteen years, had orthostatic albuminuria and chronic pentosuria. His mother had migraine. He was unusually tall and heavy for his age, and during his tenth year, he grew very rapidly. He often had stomach upsets since the age of nine. His nervous symptoms which came on at the age of eight, consisted of frequent hallucinations of hearing, vertigo, and globus hystericus on lying down in bed with the lights turned out. On getting in the upright position and turning on the lights, his symptoms disappeared.

(*c*) Elliot and Raper's[46] case deals with a young married woman, aged thirty-two years, who has had, since the age of four years, multiple discharging sinuses in the dorsum of the hand, knee, and

ankle—the latter still discharging at times. She was very nervous, had many minor aches and pains, and perspired freely under the axillæ. She always felt tired and weak. Prior to the discovery of the pentosuria she had a swollen leg with "inflamed veins." A general physical examination revealed that the patient was normal. This case illustrates the frequent marked discrepancy between the patient's symptoms and the physical findings. That a marked functional disturbance is present here and in many other pentosurics as well is apparent. Especially suspicious is the very frequent finding of great fatigue and other functional disturbances in young pentosurics of fifteen to thirty-five years of age.

Acquired Chronic Pentosuria. As pointed out above, there appears to be an inherited factor present in many cases of chronic pentosuria. However, there are some cases in which the pentosuria seems to have been acquired:

1. Blumenthal's[5] case of a banker, aged sixty-five years, is reported as having renal colic and hematuria in 1878, and a reducing substance in his urine in 1880. However, in 1887 and in 1888, no reducing substances were found in the urines. At this time, he began to have frequent dizzy spells and one attack of syncope. The patient's pentosuria was discovered about six years later.

2. Klercker's[27] first patient did not have any sugar in his urine on previous examinations, but his pentosuria was discovered following a period of great mental strain.

3. Weil's[39] second case had a small amount of "sugar" in his urine which disappeared entirely for a period of two years. After this time a chronic pentosuria set in. As reported above, his third case of a pregnant woman is of the acquired type, since her chronic pentosuria set in only after her baby was weaned, whereas during the pregnancy and lactation repeated urine examinations were negative for pentose.

4. Rosenfeld's[33] second case had been a patient of his for some years. The man was a neurasthenic, with gastric symptoms, and his urines had been previously normal—the last examination being one and three-quarter years prior to his present illness. After receiving a nervous shock in a railroad accident, he showed pentose in his urine. Both the nervous symptoms and the pentosuria gradually disappeared in two months.

5. Cohen[45] reported that for many years his patient's urine failed to show any reducing bodies on repeated examinations. This occurred prior to the onset of the pentosuria.

6. In Schüler's[44] second case, a boy aged fifteen years, complained of frequent headaches, furunculosis, nervousness, and constipation. The urine showed albumin and pentose. The patient was sent away to an outdoor school, and after nine months the symptoms, the pentosuria and albuminuria, disappeared. Six months later the urine was still normal.

7. Alexander's[58] case of intermittent pentosuria showed a definite relationship to the amount of milk ingested and to the presence or absence of an infection.

8. Levy and Pierson[63] report the finding of a normal urine when their patient was twenty-two months of age. The patient had had rickets, obesity and repeated respiratory infections before the discovery of the pentosuria at three years of age.

These 9 cases, therefore, show that chronic pentosuria behaves itself as do many other common clinical and pathological disease entities. While a hereditary factor may be present (as is also present in diabetes, hemolytic jaundice, and so forth) yet the same disease process is apparently brought on or aggravated by infections, nervous traumata, and other toxic environmental factors. When these factors were apparently removed in 3 cases, the pentosuria disappeared.

Toxic Pentosuria. The possible presence of a toxic pentosuria, that is, pentosuria brought about by drugs, has hardly received any notice since Johnstone's[32] work in 1906. Practically all reviewers of pentosurias fail to mention this type altogether. Soon after Salkowski and Jastrowitz[1] reported their first case of chronic pentosuria in a morphin addict, Reale[3] reported a second case. However, in the first case, when the morphin was stopped, the pentosuria remained, but in Reale's case the pentosuria disappeared when the morphin intake was discontinued. In 1895, Caporali[10] found 3 more temporary pentosurias while the patients were under the influence of morphin, and he also produced a pentosuria in five healthy dogs with morphin injections. In 1902, Luzzatto[17] reported another case of chronic pentosuria in a morphin addict. On the other hand, Bendix[24] maintained that in patients who are taking morphin, combined glycuronates may appear in their urines and give the pentose reactions. However, Bendix believed that the urinary pentose in the chronic type was optically inactive, and he thus ruled out Reale's patient who showed a dextrorotatory reducing substance in his urine. This objection is, however, no longer tenable as many of the recently reported cases showed d-xyloketose in the urine. Johnstone reported (from von Jaksch's Clinic) 4 cases of temporary pentosuria brought about by morphin injections. In 2 patients, continually under the influence of morphin, $\frac{1}{4}$ to $\frac{1}{2}$ liter of apple juice taken by mouth caused a very distinct pentosuria. These small amounts did not ordinarily produce a distinct pentosuria. In 2 other cases, the drinking of $\frac{1}{4}$ liter of juice alone failed to produce a pentosuria, but when 0.01 gm. of morphin was injected in addition, a distinct pentosuria set in.

On several occasions, the writer noted a marked increase in the per cent of urinary pentose after pantopon (0.04 to 0.1 gm.) was taken by mouth. At the same time small doses of amidopyrine (0.1 to 0.3 gm.) were also taken. The increase in the per cent of

pentose (from 1 to 2.2 per cent) seems, however, too great to be produced by these small doses of amidopyrine alone, and thus some of the increase may have been due to the pantopon ingested. These urines did not ferment with yeast, which seems to rule out the glycosuria that sometimes follows the intake of morphin. On January 16, 1928 (see Chart III) following the intake of pantopon (0.1 gm.) and amidopyrine (0.2 gm.) the average percentage of the urinary pentose rose from 0.42 per cent on the previous day to 1.52 per cent. On January 21 and 22 (see Chart IV) the patient took some codein phosphate, and the total twelve-hour output of urinary pentose was somewhat higher (2.2 to 2.6 gm.) than the usual amount (less than 2 gm.). These findings suggest the possibility that morphin and other opium derivatives may have the same effect on the pentosuria as that obtained with amidopyrine. However, further verification as made with amidopyrine is necessary and will be reported in the near future providing the obvious clinical difficulties can be overcome.

Discussion. Recently Garrod[61] classified chronic pentosuria along with albinism, cystinuria, alkaptonuria, and other "inborn errors of metabolism." This view has gained rather widespread acceptance, and one finds it difficult to study Garrod's thorough review without being persuaded to his viewpoint. However, he pointed out that of the six anomalies listed by him, chronic pentosuria was the most doubtful member, and he also warned that pentosuria was very frequently accompanied by nervous symptoms. Of this group, Garrod says, "The chemical error pursues an even course, and shows no tendency to become aggravated as time goes on, and they are little likely to be influenced by any therapeutic measures at our disposal." Thus to be a member of this group, the following must be present:

I. The anomaly must be constantly present from birth.

II. It must pursue an even course throughout the life of the individual without producing symptoms and harm to the individual.

III. It must be unaffected by therapy.

I. *Its Presence from Birth.* To date there has not been a single case of pentosuria reported as present from birth. Levy and Pierson[68] who followed their case from birth report that the urine was "entirely negative" at twenty-two months. Six other cases are reported where previous urine examinations were negative for sugar. In all the cases reported in children, disease processes had already been present before and at the time of the discovery of the pentosuria. Unquestionably we are dealing here with an inherited factor, but this may perhaps require as in migraine, asthma, diabetes, and so forth, an environmental insult to bring on the clinical condition.

II. *Its Even Course Throughout Life, without Becoming Aggravated and without Harm to the Individual.* Garrod does not regard

this "as an essential attribute . . . but it stands to reason that an abnormality which persists into adult and even into advanced life must be relatively innocuous." The same may be, however, said for migraine, some cases of epilepsy and other chronic ailments. The even level of the excreted pentose is no more remarkably constant than the bradycardia and other vagotonic signs found in my patient. Furthermore, as pointed out above, some cases apparently became aggravated at times and the course of the pentosuria was decidedly an uneven one. The almost constant presence of marked functional disturbances, especially in young adults, the temporary but marked organic disturbances in some cases, and its frequent association with other more or less serious organic disturbances (migraine, gastrointestinal upsets, temporary glycosurias, and so forth) should warn us against giving too good a prognosis in these cases as far as morbidity is concerned. The disappearance or the diminution of the pentosuria with the parallel disappearance or diminution of the accompanying clinical symptoms in 5 cases of chronic pentosuria rather favors a close relationship between the two.

III. *It is Unaffected by Therapy.* This assumes that the pentosuria is present at an even level and that no therapeutic measure will decrease it. In Meyer's[14] case, there was a decrease of 50 per cent of the urinary pentose and a marked improvement in his clinical condition, after the patient was placed on a moderate carbohydrate diet plus 2 liters of milk a day. This lasted for several months. A psychical trauma then reproduced the symptoms and the pentosuria rose to its former high levels. In Alexander's[54] case the symptoms and the pentosuria disappeared with a radical change in diet. In Rosenfeld's case the nervous symptoms and the pentosuria disappeared together as occurred in Schüler's case. In this writer's report the marked diminution of the pentosuria was present during a period of marked clinical improvement and during a series of non-specific protein injections. It seems, therefore, that pentosuria may be affected markedly by therapeutic measures in some cases.

At present, the most likely viewpoint is, therefore, that the pentosuria, the frequent functional, and the occasional organic disturbances accompanying it, are possibly related in some way. The writer believes that the following classification of the pentosurias will serve a more useful clinical purpose than the ones currently used:

1. Alimentary pentosuria.
2. Temporary toxic pentosuria: (*a*) Morphin; (*b*) amidopyrine?
3. Chronic pentosuria: (*a*) Congenital; (*b*) acquired.

Prognosis and Treatment. While chronic pentosuria is occasionally associated with serious organic disorders, most patients live on to old age and do not show marked nutritional disturbances. As to life then, the prognosis is good. But at the same time our prognosis should be guarded as to the morbidity of these individuals.

The futility of treating these cases in the same manner as diabetics has been emphasized long ago. At present, a moderately low-protein diet is indicated—especially when marked nervous symptoms are present. The associated disturbances (that is, migraine, intestinal disorders, and so forth) should be managed according to our current views. A thorough trial with nonspecific protein therapy may be worth while. It is very important to remember in treating the nervous symptoms of these patients that amidopyrine and opium derivatives may markedly increase the urinary pentose.

Summary. The writer has reviewed 78 cases of chronic pentosuria from the literature and has added another one. Salkowski, the discoverer of this disease, believed that we were dealing with a harmless metabolic anomaly. This viewpoint was later developed by Bendix, Bial, Janeway, and finally by Garrod who classified it along with other "inborn errors of metabolism." In favor of this viewpoint, we have several cases reported as normal, and that most patients live on for many years without marked nutritional disturbances. In addition, in some cases despite the disappearance of the clinical symptoms, the pentosuria still remains. Finally, in many cases the percentage and total output of urinary pentose are at a relatively constant level, regardless of the therapeutic measures taken. In favor of its being a clinical entity, we have the presence of nervous and other symptoms in about 90 per cent of the cases with clinical reports; the frequent association of serious derangements (temporary glycosurias, migraine, and so forth), with the pentosuria; the numerous instances where the disease seems to have been acquired; and that the clinical symptoms and the pentosuria run closely parallel to each other in some pentosurics.

In Aron's case, a boy, aged five years, whose mother had migraine and one brother had epilepsy, began to have migraine headaches with vomiting at the age of three. On examination, he had a "dry bronchial catarrh, two eczematous spots on the left arm," a palpable liver and spleen. Aron pointed out that with the migraine attacks gone, the pentosuria was still present. Therefore, there was no connection between the symptoms and the pentosuria. However, the writer does not believe that the constitutional disturbance in Aron's case disappeared entirely between attacks. In my case, between the periodic headaches, the patient was far from being well, and the bradycardia, myosis, fatigue, and some nervous symptoms still remained. This the writer has frequently noted in his other migraine patients. As Cassirer and Bamberger point out, the fact, that a neuritis comes and then disappears in the course of diabetes mellitus and leaves the glycosuria behind it, is not opposed to the clinical connection of diabetes and the neuritis.

Conclusions. 1. From the present available evidence, chronic pentosuria should be classified as a distinct clinical entity, rather than as a harmless anomaly, as is currently believed.

2. Several cases of acquired chronic pentosuria are on record.

3. It is frequently linked with migraine and a so-called vagotonic constitution. In a few instances, it has behaved clinically as other allergic diseases.

4. In the classification of pentosurias, a toxic type—due to the ingestion of opium derivatives and possibly amidopyrine—should be included.

5. Amidopyrine markedly increased the output of the urinary pentose in the writer's case. Opium derivatives may have a similar effect.

6. On one occasion in the writer's case, in the course of a series of non-specific protein injections, the patient's symptoms were temporarily relieved, and there was a marked diminution of the pentosuria during that period. Continuance of this treatment, however, was without success to date.

NOTE.—The writer is grateful to Dr. I. Greenwald for his many helpful suggestions and for his review of this paper. Above all, he is indebted to his patient whose coöperation was most unusual.

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STUDIES IN BILIARY-TRACT DISEASE.

II. A Study of the Important Microscopic Elements in Bile.

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The literature on the value of the microscopic examination of bile for the diagnosis of biliary-tract disease is extensive but conflicting. Einhorn,[1] Lyon,[2] Smithies,[3] Piersol,[4] Hollander,[5] Jones[6] and others have described the elements that they found helpful in diagnosis. On the other hand, Bassler,[7] Crohn,[8] Fitz,[9] Hartman,[10] Cutler,[11] Alvarez[12] and others have doubted the reliability of the microscopic examination of bile obtained from the duodenum. One of the chief objections raised is the fact that cellular material from the upper alimentary and respiratory tracts may be present in the bile and may lead to incorrect deductions regarding the gall bladder and gall ducts. It is evident that in order to place reliance on the microscopic examination of bile, its cellular or crystalline elements must possess characteristics that are not present in the gastric or duodenal fluids.

The present paper is a report on the presence of such elements in

bile obtained directly from the gall bladder in 100 consecutive cases of cholelithiasis, from the biliary ducts in 17 cases with a biliary fistula following cholecystectomy and from bile obtained indirectly from the biliary tract by means of a duodenal tube in 40 cholecystectomized cases. Gall bladders were not included in which the cystic duct was completely closed and the gall-bladder content was bile-free. In the cases with a biliary fistula, damage to the biliary ducts had occurred sufficient to produce clinical jaundice and the majority of the cholecystectomized cases studied by means of a duodenal tube complained of symptoms referable to the biliary tract.

To obtain a sediment for microscopic examination the bile was centrifuged for ten minutes; if it was very viscid, it was diluted with water in order to facilitate the sedimentation of suspended cellular or

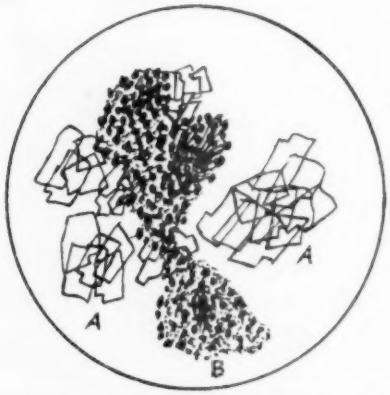

FIG. 1.—*A*, agminated cholesterin crystals; *B*, cellular débris intensely bile-stained.

crystalline material. If no sediment was obtained, the supernatant bile was examined by good illumination for the presence of macroscopic flocculi in suspension, which were "fished" out. Since the microscopic elements in bile are not present in large numbers, the slide was first examined with the low-power lens for orientation and then with the high-power or oil-immersion magnification for the study of detail.

In normal persons, all workers are agreed that the bile contains only an occasional leukocyte, epithelial cell, crystal or bacteria. In the pathologic conditions studied the bile contained the following four significant elements which do not occur in other portions of the gastrointestinal tract. It is, therefore, logical to conclude that the presence of any of these indicates a pathologic condition in the biliary system.

Constituents Indicative of Lesions in the Biliary System. 1. *Flocculi* of bile-stained columnar cells with or without bile-stained leukocytes

and colonizing bacteria enmeshed in mucus (Fig. 2). While the stomach and duodenum are lined with columnar epithelial cells, the cells in these flocculi are distinguished from the latter by their uniform degree of bile stain and their tall narrow shape with finely granular cytoplasm. Flocculi of epithelial cells from the duodenum unmixed with bile were obtained in 9 cases of mechanical obstruction of the common duct and in 5 normal cases by the injection into the duodenum of 30 cc. of 30 per cent aqueous solution of sodium chlorid. This hypertonic saline solution usually causes a spasm at the sphincter of Oddi with cessation of bile flow into the duodenum lasting from ten to fifteen minutes. The duodenal epithelial cells have a uniform appearance. They are short and cuboidal rather

FIG. 2.—Floccule of columnar cells with scattered leukocytes and colonizing bacilli.

than tall and columnar in shape, are coarsely rather than finely granular in structure and occur enmeshed in thick strands of mucus, forming a large floccule. While acid gastric juice mixed with bile in contact with flocculi of duodenal cells will cause them to take on some bile stain, it is irregularly distributed, the portions protected by the thick strands of mucus remaining unstained, which is in distinct contrast to the uniform yellow color of the flocculi from the biliary tract. Bacteria (cocci and bacilli) are frequently present in distinct colony formation incorporated in these flocculi. The cocci usually absorb the bile pigments and appear bile-stained, whereas the bacilli do not. Occasional or small groups of leukocytes are found within the same floccule but other than being bile-stained they present no characteristics to differentiate them from similar cells found in other secretions.

2. *Particles* of intensely bile-stained débris (Fig. 1*B*) usually appear macroscopically as yellow or reddish particles, pinhead in size. On microscopic examination, they are granular and intensely yellow

in color with small spots scattered throughout them, having the appearance of conglomerate cellular nuclei. These particles have been described as "bile-pigment crystals" by Jones[6] and as "bilirubin calcium pigment" by Piersol.[4] However, I believe, after having examined many of them by the oil immersion magnification, that they are cellular débris, intensely bile-stained and petrified. Enmeshed at the margin of some of them cells are seen in various stages of degeneration with the same intensity of bile stain suggesting a similar origin. In several instances, I have seen bile-stained cocci in definite long-chain formation within them, the field presenting the appearance of a stained slide of streptococci in cellular exudate in which the cytoplasm of the cells had been destroyed. Furthermore, I have never seen these particles settle out of bile on standing as crystals do, and their treatment with acid alcohol followed by chloroform, dissolves the calcium salts and pigment and leaves a scaffolding of organic detritus.

FIG. 3.—Sandlike particles consisting of a gritty mass of pigment (calcium bilirubinate) and small fragile crystals of calcium carbonate together with amorphous bile-stained material.

3. *Agminated cholesterin crystals* (Fig. 1*A*) occur as independent masses of conglomerate crystals, but more frequently they are precipitated upon flocculi of bile-stained columnar cells described under (1) or upon the particles of intensely bile-stained débris described under (2), presenting a picture of early stages in gall-stone formation, and not infrequently they appear in the form of small calculi (Fig. 1). Unless associated with the particles of stained débris, the massed cholesterin crystals are light and tend to remain suspended in the bile even after centrifugation and must be "fished" out for examination. They appear grossly as whitish pin-point-sized particles and are seen best when the bile is viewed against a dark background with good illumination.

4. *Sandlike particles* (Fig. 3) are macroscopic particles varying in size from the head of a pin to a grape seed. Their color is black, brown or red and their consistency may be gritty or pultaceous. They are heavy and readily fall to the bottom of the test tube. On microscopic examination, they consist of various crystals *en masse:* gritty, blackish pigment crystals, bile salts, carbonates, phosphates and unidentified forms together with amorphous bile-stained material. In this group the forms described by Rous, McMaster and Drury[13] in the experimental production of gall stones in animals are frequently seen, such as calcium carbonate crystals in the form of "spheroliths" and pigment masses as "pigment nuclei" and "bile thrombi."

FREQUENCY OF SIGNIFICANT MICROSCOPIC ELEMENTS IN BILE.

	Bile from the gall bladder in 100 cases of gall stones.	Bile from the biliary ducts in 17 cases of biliary fistula after cholecystectomy.	Bile from the biliary ducts obtained by a duodenal tube in 40 cholecystectomized cases.
Flocculi of bile-stained columnar cells, leukocytes and bacteria	26	6	22
Particles of bile-stained débris	88	7	14
Agminated cholestrin crystals	86	None	None*
Sandlike particles	55	2	20

* In 1 case three overlapping cholesterin crystals were seen.

Comment. Flocculi of columnar cells were present in bile from the gall bladder (26 per cent) and from the ducts (49 per cent). The columnar cells from the upper biliary ducts obtained through a biliary sinus were smaller than those from the gall bladder or the common duct. The columnar cells obtained from the common duct by means of a duodenal tube were frequently tall and in fan-shapes and could not be distinguished from those present in the gall bladder.

The particles of intensely bile-stained débris were present in the biliary ducts (37 per cent) as well as in the gall bladder (88 per cent). Besides the cases tabulated, these forms were also found in 12 cases of infectious jaundice. Therefore, although they are frequently present in the bile in cases of cholelithiasis, as has been emphasized by Piersol,[4] they are not, *per se*, diagnostic of stones.

Cholesterin crystals were occasionally seen in bile from the ducts as single or double plates of crystals, not agminated as in the gall bladder. In only one cholecystectomized case were three overlapping cholesterin crystals seen. In one cholecystectomized case, in which a postmortem examination was performed, two of the hepatic ducts were found to contain many small pigment stones, but the bile present failed to reveal any cholesterin crystals. While agminated cholesterin crystals were found only in the gall bladder (in 86 per cent of the cases of cholelithiasis), they are not positive

evidence of the presence of formed stones since they also occur in cholesterosis of the gall bladder without stones (strawberry gall bladder).

Sandlike particles occurred in bile from the gall bladder (55 per cent) and from the ducts (39 per cent). Einhorn[1] stresses the importance of these in the diagnosis of a pathologic gall bladder. However, since they are also present in bile from the biliary ducts they do not indicate the level of the lesion.

The microscopic elements in bile from the ducts obtained by a duodenal tube were much more frequent than in bile from a biliary fistula. The presence of the sphincter of Oddi in the former acting as a means of retention for these elements probably explains this difference since most of the microscopic findings were present in the first bile obtained after relaxation of the sphincter.

The correlation of the microscopic findings with the volume and color of the bile obtained in biliary drainage for the diagnosis of gross disease of the gall bladder will be the subject of the next paper.

Conclusions. 1. In the microscopic examination of bile obtained from the gall bladder and from the bile ducts, four elements are found that are diagnostic of pathologic states of the biliary tract: bile flocculi; intensely bile-stained débris, agminated cholesterin crystals, sandlike particles.

2. These elements were found in bile both from the gall bladder and from the ducts with the exception of agminated cholesterin crystals which occurred only in the gall bladder.

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STUDIES IN BILIARY-TRACT DISEASE.

III. The Diagnostic Value of a Colorimeter for the Meltzer-Lyon Test.

(Report on 100 Consecutive Cases of Gall Stones.)

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Although the Meltzer-Lyon test has been extensively employed, opinions regarding its value in the diagnosis of biliary-tract disease are still at variance. Crohn,[1] Bassler,[2] Alvarez,[3] Einhorn,[4] Jones[5] and others have doubted the diagnostic value of the segregation of bile that follows the injection of magnesium sulphate into the duodenum. Since the original publication of Lyon, the literature on the subject has become very large and need not be discussed since it has been well summarized in the recent work of Piersol,[6] Jones[5] and Lyon.[7]

In all the papers that have appeared, it is a striking fact that no concrete description has been given of the normal volume and color of the dark bile obtained in a drainage, known as "B" bile and assumed to be derived from the gall bladder. Much of the confusion in the literature may be due to this lack of fundamental definition. Since the author's first publication[8] on his experiences with biliary drainage, a colorimeter[9] of the Sahli type has been employed in which 0.7 per cent of an aqueous solution of potassium bichromate was used as a standard for the recognition and description of the "B" fraction of bile. This standard was determined to represent the maximum color of liver bile and darker bile was called "B" bile. Only the diagnostic value of this "B" bile will be considered in the present paper; a discussion of its origin will be taken up in a later publication. By dilution with water "B" bile matches the color of the standard exactly unless a large amount of biliverdin is present. Such bile on dilution takes on a greenish tint that approximately matches the standard in its content of yellow color which is sufficiently accurate for the clinical purpose of the examination. The colorimeter is examined by transmitted daylight, or if that is not available by the illumination of a microscopic substage daylight lamp at a distance of 1 or 2 inches. The color intensity of the bile is expressed by the number of times its volume must be diluted to match the standard. Thus, when the volume of water added is equal to the volume of "B" bile used the color intensity is 1; when the volume of water is twice that of the bile the color intensity is 2, and so forth. A curve of the drainage can be charted by plotting the volume of the "B" bile as abscissa and the color intensity as

ordinate (Figs. 1 to 6). I found that when the volume of "B" bile is 25 cc. or more with a color intensity of 1 or more, the gall bladder at operation was normal or approximately normal in size and appearance and was functioning through an open cystic duct. When no "B" bile is obtained (as defined below), the gall bladder at operation was grossly diseased. In the present paper, the use of this colorimeter in the Meltzer-Lyon test for the diagnosis of gall stones and of gross disease of the gall bladder will be discussed.

Technique. To determine whether the tube is in the second portion of the duodenum fluoroscopic examination is the only exact method and should be employed for accurate work in preference to the clinical tests that have been suggested.

For diagnosis, the purpose of the drainage is to obtain as much "B" bile as is possible up to the minimal amount that is normal (25 cc. with color intensity of 1 or more). The bile is obtained by siphonage and is collected in test tubes, a different tube being used for each change in the color of the "B" bile. If "B" bile is being discharged slowly, the tubing is "milked" by hand to assist its flow out of the tube. Aspiration is employed only if the bile ceases to

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FIGS. 1 TO 6.

Abscissæ: Volume of "B" bile in cc. Ordinates: Color intensity of "B" bile. Double base line: Color of the standard. Horizontal lines below base line: Bile that is not darker than the standard (volume not recorded). Irregular lines below base line: Bile free or bile tinged duodenal fluid (volume not recorded). Arrows: Injections of 30 cc. of 33 per cent magnesium sulphate.

FIG. 1.—No "B" bile. First injection: Bile tinged duodenal fluid. Second injection (ten minutes later): Bile tinged duodenal fluid. Third injection (ten minutes later): Bile tinged duodenal fluid. Fourth injection (ten minutes later): Bile is not darker than the standard. Fifth injection (ten minutes later): Bile is not darker than the standard. Sixth injection (ten minutes later): Bile is not darker than the standard.

FIG. 2.—No "B" bile. First injection: Bile is not darker than the standard. Second injection (ten minutes later): Bile is not darker than the standard. Third injection (ten minutes later): Bile is not darker than the standard.

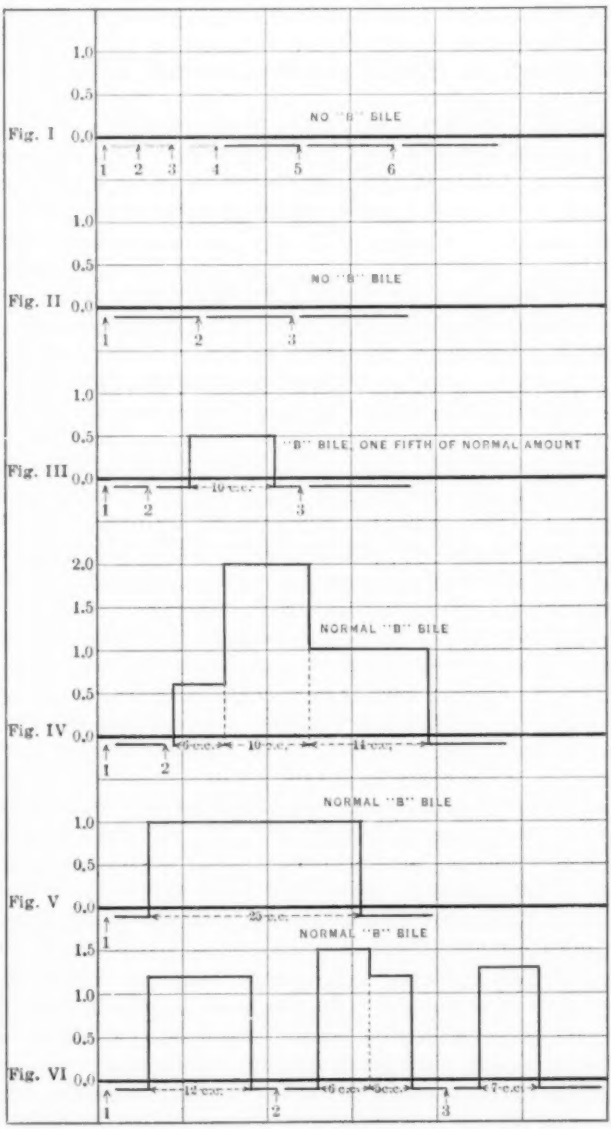
FIG. 3.—"B" bile, one-fifth of normal amount. First injection: Bile is not darker than the standard. Second injection (ten minutes later): 10 cc. of "B" bile with color intensity of ½ (equivalent to 5 cc. with color intensity of 1). Third injection: Bile is not darker than the standard.

FIG. 4.—Normal amount of "B" bile. First injection: Bile is not darker than the standard. Second injection (ten minutes later): Following amount of "B" bile obtained: 6 cc. with color intensity of 0.6 (equivalent to 3.6 cc. with color intensity of 1). 10 cc. with color intensity of 2; 14 cc. with color intensity of 1. Total "B" bile is 27.6 cc. with color intensity of 1 or more. This is in excess of the *minimal* amount for normal.

FIG. 5.—Normal amount of "B" bile. First injection: 25 cc. of "B" bile with color intensity of 1.

FIG. 6.—Normal amount of "B" bile. First injection: 12 cc. of "B" bile with color intensity of 1.2. Second injection: Following amount of "B" bile obtained: 6 cc. of "B" bile with color intensity of 1.5; 5 cc. of "B" bile with color intensity of 1.2. Third injection: 7 cc. of "B" bile with color intensity of 1.3. Total "B" bile is 30 cc. with color intensity of 1 or more. This is in excess of the minimal amount for normal.

flow to make certain that the tube is patent. If during the drainage, the character of the flow continually resembles a mixture of bile and gastric juice rather than pure bile, the position of the tube is checked



by fluoroscopic examination as occasionally the duodenal tip slips back into the stomach due to gagging or retching.

The number of injections of magnesium sulphate that is employed depends upon the amount of "B" bile that is obtained. Since more than 3 injections are frequently required, I use only 1 ounce of 33 per cent of magnesium sulphate for each injection in order to limit the quantity of salt that may enter the intestinal tract. It is worthy of note that practically all the authors who reported that biliary drainage was unreliable in diagnosis used only 1 injection of magnesium sulphate.

In normal cases "B" bile usually appears within ten minutes after an injection of magnesium sulphate. However, in some cases it does not appear until after the third injection even though good bile flow is obtained. For these reasons, when the color of the bile is lighter than the standard, 1 ounce of 33 per cent magnesium sulphate is injected three times at ten-minute intervals before concluding that no "B" bile is present. At times, especially in cases of duodenal ulcer, the ampulla does not relax until after the second or third injection and the fluid discharged is either colorless or just bile tinged. In such cases the 3 injections of magnesium sulphate are counted from the time good bile flow is first obtained (Fig. 1). If after an injection, "B" bile appears, it is collected until the color of the bile becomes lighter than the standard. The stimulation with magnesium sulphate is then repeated and the bile is again collected as described. This procedure is continued until 25 cc. of "B" bile with a color intensity of 1 or more is obtained or until no more "B" bile is discharged during a period of ten minutes following the last injection of magnesium sulphate (Figs. 3 and 6). When "B" bile is sluggishly discharged its color may be only slightly darked than the standard and its color intensity may be a fraction of 1. In order to compare its volume with that of the normal, the color intensity is raised to 1 (since the color intensity in normals is expressed as 1 or more) by reducing its volume by an equivalent fraction (Figs. 3 and 4). But if the color intensity is 1 or more the volume of the bile is equal to the amount measured since in normal cases the color intensity is so expressed. Thus 10 cc. of "B" bile with a color intensity of 2 is expressed as such and is not equivalent to 20 cc. of bile with a color intensity of 1 (Figs. 4 and 6).

Microscopic Examination. In a previous paper, it was pointed out that agminated cholesterin crystals were derived from the gall bladder. Other abnormal microscopic elements which occur in inflammatory states of the biliary system such as flocculi of bile-stained columnar cells with or without leukocytes and bacteria enmeshed in mucus, particles of intensely bile-stained cellular debris and sandlike particles were found in bile both from the ducts and from the gall bladder. For brevity of description, the latter will be grouped as duct elements in distinction to the agminated cholesterin crystals which occurred only in the gall bladder. Whether, in a

particular case the duct elements originated from the gall bladder or from the biliary ducts cannot be determined. However, for practical purposes such differentiation is not essential since recent investigation[10,11] has proven that cholecystitis is not an isolated entity but is associated with inflammatory changes in the liver and biliary system.

Diagnosis. The following analysis is based on the findings by biliary drainage and at operation in 100 consecutive cases of cholelithiasis. Patients with clinical jaundice were excluded from this series since jaundice due to a mechanical or inflammatory obstruction of the bile ducts interferes with the flow of bile and for comparison of the drainage with the normal, free flow of bile into the duodenum is necessary.

The diagnosis of cholelithiasis or of gross disease of the gall bladder was found to depend not alone on the presence of agminated cholesterin crystals, but especially on the volume and color intensity of the "B" bile. The cases can be divided into the following groups.

I. No "B" bile (48 cases).

Microscopic Examination. No clumped cholesterin crystals. Duct elements present in 39 of the cases.

Findings at Operation. Either the cystic duct was occluded or the gall bladder was found to be grossly diseased. In all these cases, calculi were present. It is worthy of repetition that a gall bladder may contain small calculi which are not palpable to the surgeon for in 2 of these cases the gall bladder appeared normal to sight and touch but on removal of the organ fine calculi, the size of grapeseed, were present at the neck of the gall bladder and in the cystic duct.

II. "B" bile present up to 5 cc. with color intensity of 1 or more ($\frac{1}{5}$ of normal amount of "B" bile) (12 cases).

Microscopic Examination. Cholesterin crystals *en masse* present in 7 and absent in 5 cases. Duct elements present in all cases. In the 5 cases in which colesterin crystals were absent, the drainage was repeated to verify the findings and in 1 case with obstruction at the neck of the gall bladder no "B" bile was obtained on repetition of the test.

Findings at Operation. In the 7 cases in which agminated cholesterin crystals were present, the gall bladder was filled with combination stones and only a small amount of bile was present. In 2 of the 5 cases without cholesterin crystals, the gall bladder contained many pigment stones and a small amount of bile. In the remaining 3 cases, the gall bladder was occluded by a stone at the neck of the organ.

The occasional appearance of a small amount (up to $\frac{1}{5}$ of the normal amount) of "B" bile in cases of occlusion of the gall bladder or in cases after cholecystectomy[9] is open to two interpretations: either the liver under certain conditions can secrete a small volume

of dark bile or the gall bladder epithelium which descends for a variable distance into the cystic duct, may be present beyond the point of block or resection and may maintain its concentrating activity. The presence of the block high up at the neck of the gall bladder in the cases mentioned is more in keeping with the latter explanation. However, whether or not "B" bile is derived from the gall-bladder epithelium, for diagnostic purposes the amount of "B" bile present in these cases was too small to be confused with the amount obtained in normal gall bladders.

III. "B" bile present, 5 to 20 cc. with color intensity of 1 or more ($\frac{1}{5}$ to $\frac{4}{5}$ of the normal amount of "B" bile) (32 cases).

Microscopic Examination. Agminated cholesterin crystals present. Duct elements present.

Findings at Operation. The gall bladder was thickened, the cystic duct was open and the gall bladder contained bile and calculi. *In cases in which the volume of "B" bile is below normal and no cholesterin crystals are found repetition of the drainage is indicated to corroborate the findings.* In 2 cases, not included in the series of cholelithiasis, in repeated tests only $\frac{1}{5}$ to $\frac{2}{5}$ of the normal amount of "B" bile was obtained without the presence of cholesterin crystals. At operation, the gall bladder was surrounded by dense adhesions which in 1 case arose from a large penetrating duodenal ulcer.

IV. "B" bile present in normal amount (25 cc. with color intensity of 1 or more) (8 cases).

Microscopic Examination. In 4 cases agminated cholesterin crystals precipitated upon particles of bile-stained debris were present. In 2 cases only duct elements were found. In 2 cases the microscopic examination was negative.

Findings at Operation. The gall bladder was normal or practically normal in size and shape and was functioning through an open cystic duct.

In the 4 cases in which agminated cholesterin crystals were present, the gall bladder contained numerous small stones. Similar findings by drainage were also obtained in several cases of cholesterosis of the gall bladder without the presence of formed stones. In these cases, the bile contained varying numbers of the particles like those that had been obtained by biliary drainage, consisting of cholesterin crystals precipitated upon bile-stained debris presenting a picture of an early stage in gall-stone formation.

In the 2 cases in which duct elements but no cholesterin crystals were present, it was concluded from the drainage that there was an inflammatory reaction within the biliary tract but that there was no evidence of stones. However, at operation small stones were present: in 1 case four jackshaped pure pigment stones each the size of an orange pit, and in 1 case twelve grapeseed-sized calculi of the combination type.

In the 2 cases in which the microscopic findings were negative it was concluded that there was no evidence of biliary-tract disease but at operation single pure cholesterin stones were present, the size of a grape.

In 18 other cases in which the amount of "B" bile obtained was normal and the microscopic findings were negative or showed only duct elements, the gall bladder at operation appeared grossly normal and no stones were present.

Other than the cases of cholesterosis of the gall bladder without formed stones, in which the bile contains macroscopic particles of agminated cholesterin crystals precipitated on bile-stained debris, the diagnosis of cholecystitis without stones in which the gall bladder at operation appears normal, will not be discussed, since this diagnosis is open to a latitude of interpretation. As Eusterman[12] states in discussing the diagnostic accuracy of cholecystography: "The pathologic criteria might be too conveniently elastic and any gross or microscopic deviation from the normal, no matter how trivial could easily be interpreted as due to pathologic change." This admonition holds particularly true regarding the interpretation of pericholecystic adhesions. Bryant[13] found that the gall bladder is the most frequent site of congenital bands and adhesions within the abdomen. At operation, however, the gall bladder is frequently removed because of their presence even though no induration of the walls nor interference with the function of the organ is present.

Conclusions. 1. The bile obtained by duodenobiliary drainage was examined microscopically and by means of a colorimeter for the determination of the volume and color intensity of the "B" bile in 100 consecutive cases of cholelithiasis.

2. With the technique described, drainage presented evidence of a pathologic gall bladder in 96 per cent of the cases.

3. Gross disease of the gall bladder was present when the following findings were obtained: (*a*) No "B" bile; (*b*) $\frac{1}{5}$ to $\frac{2}{5}$ of the normal amount of "B" bile without cholesterin crystals; (*c*) $\frac{1}{5}$ to $\frac{4}{5}$ of the normal amount of "B" bile with agminated cholesterin crystals.

4. When the amount of "B" bile was normal the gall bladder at operation was normal or practically normal in size and shape and was functioning through an open cystic duct. When agminated cholesterin crystals precipitated upon particles of bile-stained debris were present in these cases, cholesterosis of the gall bladder with or without formed stones was found. In 4 per cent of the cases of cholelithiasis in which small calculi were present in a normal-sized gall bladder, the amount of "B" bile was normal and agminated cholesterin crystals were absent.

ON THE RELATION OF GALL BLADDER EMPTYING TO THE INGESTION OF FATS: II.*

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The present communication is a report on a series of experiments made as a continuation of work previously described, in which a study was made on the relative effect of various fatty substances on the emptying of the gall bladder. In this earlier work,[1] which was suggested by the studies of Boyden, we investigated the effect on gall bladder emptying produced by the ingestion of egg yolk, total egg lipoids (free from protein), egg lipoids from which the lecithin had been removed, and egg lecithin. The possible influence of absorption of emulsified fat was also considered and a few experiments were made in which olive oil was given. In this earlier investigation, we also made observations on the possible relations between fat absorption and gall bladder emptying. To this end, samples of blood were taken before and at intervals after the administration of lipoids and the samples of blood analyzed for total fatty acids.

As a result of this work the conclusions were made that gall bladder emptying was only slight following unemulsified fat (olive oil); that egg yolk produced a more rapid and complete emptying than did cream or olive oil; and that no fat ingredient contained in egg yolk was found to be specific for the gall bladder response. Any one of several above mentioned produced emptying of the gall bladder.

The blood analysis showed no relation between the quantity of blood fat and the emptying time of the gall bladder.

In this paper we wish to present the results of a series of experiments in which some of the products of egg yolk and of cream were administered. The products used were:

1. A preparation of the fatty acids of butter. Butter was heated with a solution of sodium hydroxid until completely saponified. The mixture was then acidified with sulphuric acid and the resulting mass of solid fatty acids repeatedly washed with hot water until all sulphuric acid had been removed. Thirty grams of this fatty acid preparation were emulsified by means of 4 gm. of gum arabic dissolved in 100 cc. of water. The mixture was shaken rapidly in a shaking machine for four hours. A permanent emulsion was thus

* Read before the Thirty-first Annual Meeting of the American Gastro-enterological Association, Washington, D. C., April 30 and May 1, 1928.

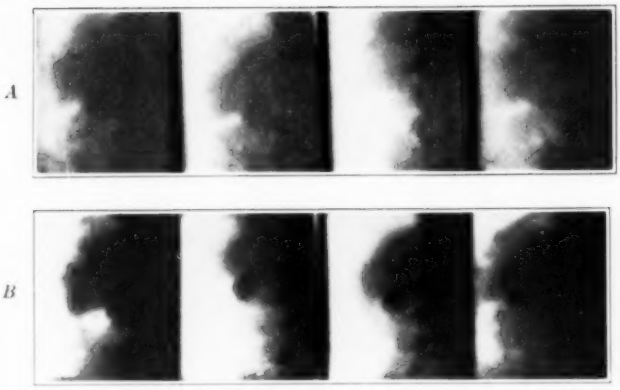

FIG. 1.—*A*. Disappearance of shadow following ingestion of egg yolk. *B*. Persistence of shadow following ingestion of fatty acids and glycerol (from egg yolk).

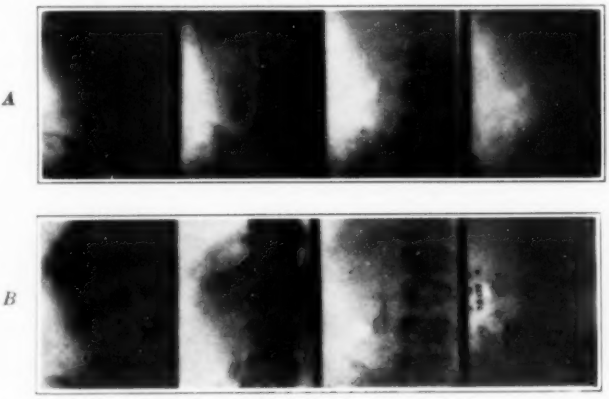

FIG. 2.—*A*. Disappearance of shadow following ingestion of egg yolk. *B*. Persistance of shadow following ingestion of fatty acids and glycerol (from egg yolk).

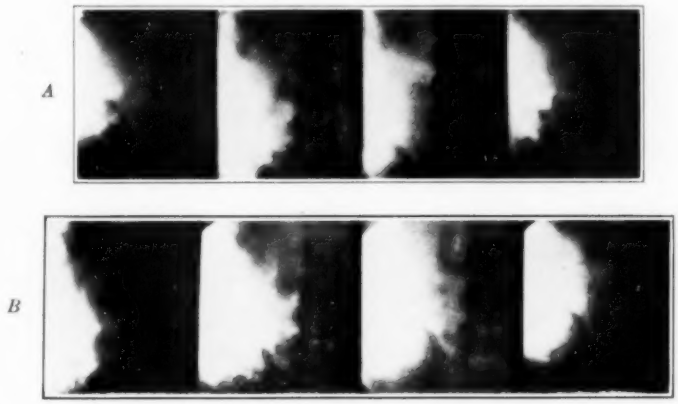

FIG. 3.—*A*. Disappearance of shadow following ingestion of egg yolk. *B*. Persistence of shadow following ingestion of fatty acids and glycerol (from egg yolk.)

product which was administered by mouth after flavoring with a few drops of extract of peppermint.

2. A preparation of emulsified fatty acids prepared as above to which was added pure glycerol in the preparation of 1 to 10 gm. of fatty acid.

3. A preparation of the total fatty acids from egg yolk. The total lipoids of egg yolk were prepared by repeated extractions at room temperature of the yolks of 40 eggs with a mixture of one part butter and two parts 95 per cent alcohol. The various extracts were united, the solvent distilled off and the resulting mass of lipoid material saponified with sodium hydroxid. The free fatty acids were then liberated by the addition of sulphuric acid, were repeatedly washed to remove the mineral acid, and were finally emulsified as described above.

4. A preparation of emulsified-egg fatty acids prepared as above to which was added 1 gm. of pure glycerol for each 10 gm. of fatty acid used.

5. In order to check the effect of artificial emulsions we used on a few patients, a commercial preparation of liquid petrolatum emulsified with agar.

Procedure. Individuals were selected who gave no evidence of gall bladder disease.

The gall bladder was visualized by the oral administration of 3.5 gm. of sodium tetraiodophenolphthalein. Patient fasting, plates were made fourteen and sixteen hours respectively after administration of the dye. The fat preparations were given by mouth and subsequent plates were made one and two hours respectively thereafter.

The effects of fatty acids derived from butter and from egg yolk were noted on several individuals. The gall bladder failed to empty in each and every instance.

A comparative study was made on the same individual of the effect of the administration of egg yolks and later of the digestion products of egg yolks (fatty acids and glycerol). In each individual so studied, it was observed that there was a marked emptying of the gall bladder following the taking of the egg yolks, whereas the predigested fat (fatty acids and glycerol) showed no response (Figs. 1, 2 and 3).

Summary. The emptying of the gall bladder is apparently not dependent upon fat absorption as far as can be determined by blood analyses.

Since the already digested fat does not affect the gall bladder reflex, there is suggested some relationship between gall bladder emptying and the intestinal digestion of fat.

We wish to express our appreciation for the coöperation of the Radiological Department, Touro Infirmary.

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CARDIOSPASM WITH SPECIAL REFERENCE TO ETIOLOGY.*

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The etiology of cardiospasm is obscure. The older writers differentiated between the idiopathic and reflex type as well as between the acute intermittent and chronic permanent spasm. This paper was primarily intended to report cases of cardiospasm associated with pathologic conditions in other organs which might indicate an etiologic significance. However, a perusal of the literature reveals that the question of treatment is by no means a settled one. The work of Plummer, as well as that of many of the members of this Association (notably the Symposium in 1911[1] participated in by Einhorn, Jesse Myer, Willy Meyer, Meltzer, Morgan and others) seemed to place the treatment on a secure definite basis. They concluded that medicines were useless in the treatment of true spasm of the cardia; that the ideal efficient treatment was a series of gradual intermittent dilatations by means of rubber balloon dilators operated by hydrostatic or pneumatic pressure; that surgery was rarely, if ever, indicated.

Recently surgery has been advocated by Heller,[2] Geffert,[3] Crone-Münzebrock,[4] Lotheissen,[5] Thieding[6] and others. Emerson[7] used a Barnes obstetrical bag for forcible divulsion of the cardia. Eschbaum[8] recommends an inflated rubber bag pulled forcibly through the cardia. Starck[9] devised a metallic instrument which forcibly divulsed the cardia. Maydl[10] used Starck's method successfully in 4 cases but the fifth patient succumbed to rupture of the cardia.

The most exhaustive recent study of cardiospasm is that of Thieding.[11] He states that the etiology may be traced to a functional disturbance in the vegetative nervous system. Among the exciting causes he enumerates ulcer, trauma, hysteria, endocrine dysfunction, gout, uremia, enteritis, tobacco, lead, lues and infectious diseases.

McCrae[12] made a critical review of the anatomy and physiology of the nerves of the cardia and came to the conclusion that cardiospasm is a result of a disturbance in the controlling nerve apparatus. He advocates surgery.

Schindler[13] regards cardiospasm as psychogenic. He states that psychotherapy will cure in the early stage but dilatation is necessary in cases of long standing.

* Read at the Thirty-first Annual Meeting of the American Gastroenterological Association, Washington, D. C., May, 1928.

FIG. 1.—Cardiospasm in female, aged sixty-seven years. The esophagus was tremendously dilated, holding 1500 cc. Good recovery with pneumatic dilator. Second Roentgen ray film secured four years later showed no diminution of the dilatation of the esophagus.

FIG. 2.—Case of acute spasm in male, aged forty-nine years, suffering from spinal arthritis. Film was secured during an attack of pain.

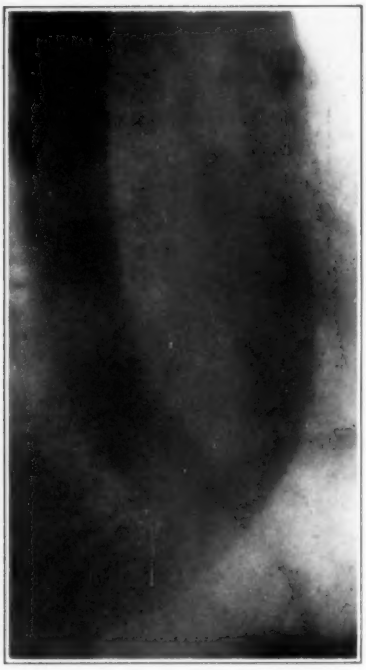

FIG. 3.—Patient with achylia gastrica who was taking unusually large doses of hydrochloric acid. Roentgen ray revealed cardiospasm which subsided after withdrawal of the acid.

FIG. 4.—Severe recurrent spasm in patient with tabes dorsalis, aged twenty-one years. First attack in 1914. Recovery after dilatation. Second attack in 1917. Third attack in 1925.

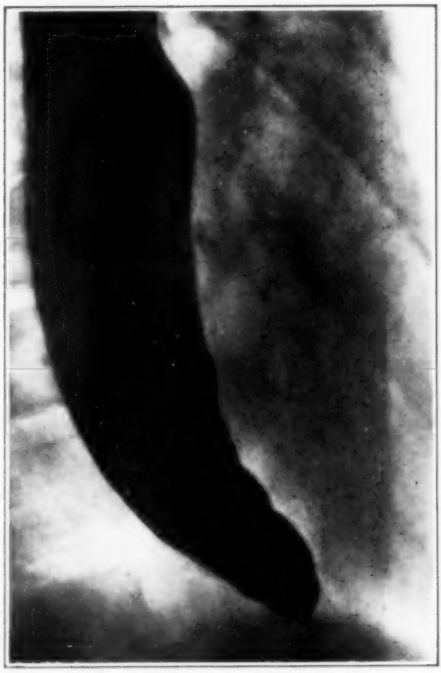

FIG. 5.—Cardiospasm in female, aged fifty years. She made good response to dilatation. Had basal rate of +25 but gained weight so rapidly that her thyroid symptoms were overlooked until six months later, when thyroidectomy became necessary.

FIG. 6.—Female, aged thirty-five years, had been under observation for bronchial asthma for four years. Finally developed symptoms of cardiospasm and responded well to treatment by hydrostatic dilator.

FIG. 7.—Cardiospasm associated with carcinoma of the cardiac end of the stomach in male, aged fifty-nine years. Esophagoscopy showed cardia not involved in the growth. The spasm responded well to dilatation by pneumatic dilator. Ultimately metastasis and exitus.

Plummer[11] reports 12 cases of cardiospasm without diffuse dilatation associated with gross lesions of the stomach—of these 2 patients had ulcer, 2 syphilis, 5 carcinoma, 3 cases of suspected but not demonstrable ulcer.

Jesse Myer[15] implicated enteroptosis as an etiologic factor.

Heysorsky[16] reports 6 cases connected with gastric ulcer.

Fitzgibbon[17] reports 1 case and Vinson[18] reports 2 cases of cardiospasm concomitant with esophageal diverticulum. Dessecker[19] in 8 cases of diverticulum of the lower third of the esophagus found associated cardiospasm in 5 of the patients.

Moore and Vinson[20] report a case of cardiospasm with kinking of the esophagus as a result of kyphosis.

Mosher's[21] anatomical studies lead him to conclude that no true spasm is present in so-called cardiospasm, but that the difficulty in swallowing is produced by a mobilization and displacement of the terminal portion of the esophagus. In many cases a ptosis of the diaphragm is present.

Verbrycke[22] in his investigation believes that the sympathetic fibers of the vagus supplying the cardia are at fault. He gives as probable causes neurotic, psychic, reflex, irritative and toxic.

This study is based on 60 cases of cardiospasm, of which 29 are included in the following table. The slight degree of spasm found in routine Roentgen ray examinations is not included in this number. In 29 of the patients pathologic conditions were found in other organs. Thirty-one of the patients presented no disease conditions in other organs. Therefore, they are not included in this table.

The hyperthyroid patients presented themselves with the symptoms of cardiospasm predominating. All were much emaciated. Treatment by dilatation of the cardia produced rapid improvement and gain in weight. Later on the hyperthyroid symptoms came into the foreground with final resort to surgery and ultimate recovery.

The gall-stone patients developed symptoms of spasm of the cardia before the diagnosis of gall-bladder disease was established. The attack came on some months after recovery from the cardiospasm. One of our patients came in for general diagnosis presenting no symptoms excepting undue fatigue. Gall stones and a mild degree of cardiospasm were revealed in the Roentgen ray films. We believe that this patient will ultimately develop symptoms of both spasm and gall stones.

A review of the literature reveals a remarkable unanimity among all observers that disturbances in the nervous mechanism of the cardia are responsible for the production of the spasm. Lesions in the stomach near the cardia have been mentioned as probable exciting factors. We have shown that a large variety of pathologic conditions may coëxist with cardiospasm. Our findings suggest a probable etiologic significance. The cases of early acute spasm mentioned above are of particular interest in this respect.

Case No.	Sex.	Age.	Type of spasm.	Direct treatment.	Result.	Diseases in other organs.
1	M.	49	Acute	Diet of soft food	Recovery	Spinal arthritis, involving fifth left intercostal nerve.
2	F.	50	Acute	Pneumatic dilator	Recovery	Ulcer of greater curvature of stomach.
3	F.	65	Acute	Withdrawal of HCl	Recovery	Achylia gastrica; was taking large doses of HCl.
4	M.	21	Chronic*	Pneumatic dilator	Recovery	Tabes dorsalis; first attack in 1914, again in 1917 and 1925.
5	F.	36	Chronic	Pneumatic dilator	Recovery	Neurosyphilis.
6	F.	50	Chronic	Pneumatic dilator	Recovery	Exophthalmic goiter.
7	F.	64	Chronic	Pneumatic dilator	Recovery	Exophthalmic goiter.
8	F.	29	Chronic	Pneumatic dilator	Recovery	Exophthalmic goiter.
9	F.	45	Chronic	Pneumatic dilator	Recovery	Gall stones.
10	F.	39	Chronic	Pneumatic dilator	Recovery.	Gall stones.
11	F.	60	Chronic	Pneumatic dilator	Recovery	Gall stones.
12	F.	56	Chronic	Pneumatic dilator	Recovery	Gall stones.
13	F.	52	Chronic	Pneumatic dilator	Recovery	Ulcer cardia
14	M.	48	Chronic	Pneumatic dilator	Recovery	Ulcer cardia.
15	M.	62	Chronic	Hydrostatic dilator	Recovery	Spinal arthritis.
16	F.	35	Chronic	Hydrostatic dilator	Recovery	Bronchial asthma.
17	F.	26	Chronic	Pneumatic dilator	Recovery	Ulcer duodenum.
18	M.	39	Chronic	Pneumatic dilator	Recovery	Ulcer duodenum.
19	M.	42	Chronic	Pneumatic dilator	Recovery	Ulcer duodenum.
20	M.	59	Chronic	Pneumatic dilator	Exitus	Carcinoma stomach near cardia.
21	F.	60	Chronic	Pneumatic dilator	Recovery	Hypertrophic cirrhosis of liver.
22	F.	39	Chronic	Pneumatic dilator	Recovery	Pleural contractures.
23	M.	45	Chronic	Pneumatic dilator	Recovery	Pleural contractures.
24	F.	50	Chronic	Pneumatic dilator	Recovery	Pleural contractures.
25	M.	60	Chronic	Hydrostatic dilator	Recovery	Pleural contractures.
26	F.	42	Chronic	Pneumatic dilator	Recovery	Large ovarian cyst.
27	M.	39	Chronic	Pneumatic dilator	Recovery	Pyloric ulcer.
28	M.	65	Chronic	Not dilated	Exitus	Carcinoma of stomach.
29	F.	68	Chronic	Not dilated	Exitus	Carcinoma of stomach.

* Three separate attacks.

Some observers differentiate a type of atony and esophageal dilation not associated with spasm. We have never recognized such a condition. In our opinion the degree of dilatation of the esophagus depends upon the length of time the spasm has existed. In spasm of long duration, the esophagus may be tremendously dilated. This dilatation may persist for years after the spasm has been overcome, without producing symptoms, as demonstrated in one of our patients not listed in the above table. She was sixty-seven years of age and came under observation in 1924. She was extremely emaciated, weight 120 pounds. The esophagus was much dilated holding 1500 cc. of liquid. She responded well to dilatation and has remained well since. Present weight 214 pounds. A Roentgen ray film was secured four years after treatment, showing no diminution in the size of the dilated esophagus (Fig. 1).

Summary. 1. This paper is based upon a study of 60 cases of cardiospasm, of which 29 revealed pathologic conditions in other organs.

2. It appears that the nervous mechanism that controls the cardia may be disturbed by a large variety of pathologic conditions. The more closely we study our cases and search for disease elsewhere, the more rarely will the diagnosis of idiopathic cardiospasm be made.

3. Surgery is rarely if ever indicated. The spasm yields readily to dilatation by either pneumatic or hydrostatic rubber-balloon dilators.

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THE EFFECT OF IRRITATION OF THE COLON ON THE EMPTYING TIME OF THE STOMACH.*

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It is well recognized that the activity of the colon increases after the ingestion of food, but whether this is due to a true gastrocolic reflex or whether it is to be explained on Alvarez's gradient theory,

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is not known. A reverse relationship, between the ileocecal region and the stomach has been postulated from time to time. L. G. Cole,[1] in 1913, advanced the idea of a reflex from the distended terminal ileum to the gastroduodenal area, resulting in a diminution of duodenal peristalsis. A. E. Barclay[2] expressed the same idea in the following year, "the ileopyloric reflex . . . is a reflex from the last coil of the ileum back to the pylorus, a message to indicate that as much food has come to this point as can be dealt with and calling for the shutting off of the supply, the response being a quieting down of the peristalsis and a closing of the pylorus."

That irritation of the peritoneal surface produces pylorospasm has been shown by several investigators. Hughson,[3] for example, found that traumatization of any abdominal viscus in dogs increased the emptying time of the stomach approximately 67 per cent for a period of two weeks. The motility of the stomach was unaffected except that the speed of the contraction waves was increased. Barber and Stewart,[4] demonstrated that peritoneal irritation influences the activity of the whole stomach as well as producing pylorospasm.

The gradient theory of Alvarez affords a ready explanation of the frequently reported influences on the stomach of irritation of the lower intestinal tract. Temporarily, the irritated portion has a higher potential, and the gradient is turned about, inhibiting peristalsis above, or even causing reverse waves. Alvarez[5] asserts that food introduced into the rectum retards the progress of material coming down from above and believes that an enema, immediately following a meal, is likely to cause colic, nausea, and, in sensitive persons, even vomiting. Rolleston and Jex-Blake[6] reported that of 96 patients with gastric ulcer who were fed by rectum alone for a short period of time, 26 vomited on one or more occasions. Bine and Schmoll[7] had similar experiences and advised against the use of enemas in cases of fecal vomiting, chiefly among hysterical individuals, some of whom in a very few minutes would vomit suppositories or test dyes introduced by rectum. Langmann[9] collected a similar group of cases, and attributed the phenomenon to enterospasm and antiperistalsis, Grutzner[10] injected normal salt solution holding in suspension hair, powdered charcoal, or starch grains, and found that it was carried upward into the small intestine, and even entered the stomach.

Many clinical observations suggest that disturbances in the ileocecal region affect the pylorus. Aaron[11] induced pylorospasm and epigastric pain by pressure over the appendix during the fluoroscopic examination of his case. Thorning and Smith[12] saw retrograde peristalsis in the second and third portions of a dilated duodenum, shown at operation to be due to obstruction in the ileocecal region. Finney and Friedenwald[13] recognize appendicitis as a cause of pylorospasm and thereby explain its gastric upsets. Cole[14] reported several cases in which he felt that permanent changes had taken

place in the pylorus as a result of chronic appendicitis. Barclay[2] studied cases of duodenal irritation without demonstrable ulcer, and found that, "the stomach begins to empty rapidly, overloading the small intestine. In a short time (three-quarters of an hour) the stomach is empty (with a small quantity of food). Yet when a reasonably large meal is given, there is actual delay in emptying, 50 per cent residue at seven or eight hours. These cases show that when the food reached the terminal ileum the rapid emptying and general activity of the stomach ceased, and in each case there was definite ileal stasis, with very little food passing on into the cecum. Those cases that have been operated on have all shown definite evidence of old inflammatory changes in the ileocecal region."

Robinson,[15] Kellogg[16] and Case,[17] believe that an ileal stasis may cause a drag on the root of the mesentery, producing obstruction at the junction of the duodenum and jejunum, and this accounts for the gastric stasis observed.

White,[18] however, found that simple mechanical distention of the colon in cats and in men had no effect on the emptying of the stomach. Irritation of the colon with various chemicals, such as turpentine, croton oil and mustard oil, gave various results. Intense irritation caused prompt reverse peristalsis in the stomach. In some cases, marked irritation produced pylorospasm with a resulting delay in the emptying time, whereas, in others it produced hyperperistalsis with rapid emptying of the stomach. Moderate irritation had no effect whatever. He also reported that of "42 cases without important lesion in the stomach" but with definite ileal stasis by Roentgen ray, only 4 showed a six-hour residue in the stomach, White, therefore, did not confirm Barclay's observation, and further asserted that pylorospasm due to chronic appendicitis is variable and uncertain. In 7 cases of chronic ulcerative colitis, 3 others of tuberculous colitis, and 5 carcinoma of the colon, he found no delay in the emptying time of the stomach. His conclusion is that the gastric symptoms in intestinal cases are not the result of slow emptying as a rule, but are largely toxic, or the result of referred pain or distress.

It seems clear from the literature that irritation of a peritoneal surface will cause spasm of the pylorus. Under certain conditions, material can apparently make its way from the lower to upper portions of the tract. Reverse peristalsis also seems to occur at times as a result of disturbances low down. Except for White's work there has been no attempt to determine what mechanism of the intestine needs to be involved to produce the effects observed clinically. In other words, have these disturbances been due to irritation of the mucosa or have the conditions present involved other layers of the intestinal wall? With this in mind, the writers set about producing a chemical irritation of the colon and studying its effect on the emptying time of the stomach.

Experiments. Dogs were chosen for this work because they are practically omnivorous and are easy to work with. The rate of emptying of the stomach was determined by the Roentgen ray, as this is practically essential, if opening of the abdomen is to be avoided. This rate should vary from the normal, if gastric peristalsis or the condition of the pylorus are influenced in any way.

The emptying time of the stomach under normal conditions was determined first. The animals were housed in large cages, with plenty of room for exercise. They were given a daily diet of approximately 400 gm. of boiled horse meat and 150 gm. of bread. The opaque meal consisted of 50 gm. of chopped meat, 30 gm. of bread and 20 gm. of barium sulphate, mixed in a bowl with enough water to cause the barium to adhere to the food. The dogs received this meal at 3.30 P.M. having been starved since the previous day. They were then kept without water to drink, and Roentgen rayed at intervals until the stomach was empty.

The emptying time fluctuated considerably when the animals were unused to the procedure and it required numerous observations extending over several weeks, before an average normal was established.

When the colon was to be irritated, the dog was given ½ gr. of morphin sulphate subcutaneously, and the skin was well protected by a thorough application of petrolatum. A 15 to 20 per cent mixture of spirits of turpentine in water and barium sulphate was then injected slowly into the rectum by means of a small catheter. This was continued until fluoroscopic examination showed that it had reached the ileocecal valve. Thereupon, the injection was discontinued but the enema allowed to remain for several minutes before removal. The emptying time of the stomach was not determined for at least a day after injection, in order to avoid any possible effect from the morphin.

Dog A was studied in December, 1926. Twelve observations gave an average emptying time of the stomach of four and a half to five hours. January 11, 1927, the colon was irritated and for the next few days the animal appeared quite ill. January 17, the emptying time was four to four and a half hours, and several more studies agreed. This suggested a slight decrease in the emptying time from the normal, though perhaps too slight to be significant. It was felt that six days might be too long to wait before reëxamination, despite the fact that there was a considerable amount of mucus in the stools for two weeks after this one injection. Moreover, the radiographic method of using films, employed hitherto, had not proven entirely satisfactory, as the barium in the intestine prevented an accurate determination of the emptying time by obliterating small amounts in the stomach. It was, therefore, decided to reëstablish the rate of emptying by the fluoroscopic method. During the next two months this proved to average five to five and a half hours.

This was somewhat longer than before, but we felt that it was more accurate.

Dog A was again irritated on March 7 and 11, and on March 16 his emptying time was five and three-quarter hours. March 18 it was six and three-quarters hours. These results suggested a slight increase in the rate of emptying. Two other dogs were, therefore, prepared and all three studied. The following table illustrates the results:

EMPTYING TIME OF STOMACH BEFORE AND AFTER IRRITATION OF THE COLON.

	Dog A.	Dog B.	Dog C.
Emptying time of stomach	5 hrs.	5½–6 hrs.	5½–6 hrs.
Colon irritated			
Colon irritated again (2 days later)	..	..	(not repeated)
Next day	7½ hrs.	..	5½ hrs.
3 days after	5½ hrs.	6 hrs.	6 hrs.
5 days after	..	6¼ hrs.	
8 days after	6 hrs.	5¼ hrs.	
14 days after	..	..	6½ hrs.*
16 days after	..	..	5 hrs.*

* In this dog the colon was again irritated fourteen and sixteen days after the first irritation.

Discussion. These results show that irritation of the colonic mucous membrane does not influence the rate of emptying of the stomach, and confirms White's work fully. In other words, a chemical inflammation strictly limited to the mucosa, not extending above the ileocecal valve, and at least as severe as might occur in any human condition, has no appreciable effect on the pyloric mechanism or gastric peristalsis, insofar as these may be studied by the ability of the stomach to discharge its contents.

So far as this work goes, it would suggest that the so-called gastric symptoms occurring in cases of simple colitis are not in fact produced by the stomach at all. This is not inconceivable, for it has never been proved that the symptoms, which are attributed to the stomach, are produced by that organ. It has only recently been shown that the heartburn, which was once thought to be gastric in origin, is caused by the esophagus. Possibly the gastric stasis observed clinically in cases of colitis may be due to involvement of the peritoneum. Then again, cases diagnosed as simple colitis may have an enterocolitis, and the gastric stasis be due to the irritation of the ileal mucosa. Further work should be done on this point.

Summary. There are numerous instances in the literature suggesting that pathology in the colon or ileocecal region may affect the gastropyloric mechanism, resulting in a prolongation of the emptying time of the stomach.

The present study, undertaken on dogs to determine if a simple but severe chemical (turpentine) irritation of the mucous membrane of the colon would produce this effect, produced no change in the emptying time of the stomach.

Irritation of the colonic mucosa, therefore, does not alter gastric peristalsis or the pylorus insofar as the emptying time is concerned. Whatever relationship exists between disorders of the lower intestinal tract and the stomach must rest upon some other basis.

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A ROENTGEN RAY STUDY OF A GROUP OF LONG-DISTANCE RUNNERS.*

With Special Reference to the Effects of Exercise on the Size of the Heart.

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Considerable interest has been aroused in recent years concerning the effect of prolonged strenuous effort on the heart, lungs and bloodvessels; of special interest has been the question of cardiac hypertrophy and dilatation. The evidence for or against the occurrence of circulatory disturbances is reviewed by MacKenzie,[1] Bainbridge,[2] Abrahams,[3] Pratt[4] and others.[5] So far as we are aware, there are no studies to prove that in the normal individual

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arteriosclerosis, pulmonary infections, certain changes of the bones or sudden death are caused directly by athletic training or competition. Apparently, when these phenomena have occurred, the athletes were unqualified physically for strenuous effort, and exercise merely exerted a precipitating influence.

The present roentgenographic study was undertaken to determine the effects of long-distance running in 23 athletes. In a race from Los Angeles to New York, these runners averaged 41 miles daily for eighty-four consecutive days. The Roentgen ray study seemed to offer a fairly satisfactory means for investigating certain phenomena. Since it was only possible to make roentgenographic exposures of the runners after the race, the data are used for comparison with normal standards.

The exposures made three days after the end of the race were as follows: stereoroentgenograms of the chest at a distance of 4 feet, postero-anterior and lateral teleoroentgenograms at 7 feet, lateral views of the ankles and knees, antero-posterior views of the legs, forearms and wrists.

ROENTGEN RAY MEASUREMENTS OF THE HEART AND CHEST.

Running No.	Weight, kg.	Height, cm.	Age, yrs.	Average transverse diameter for height.*	Average transverse diameter for weight.	Predicted transverse diameter, height and weight.	Actual transverse diameter.	Variation from predicted diameter.	Intrathoracic width.	Cardiothoracic ratio.
133	75.00	189.5	34	13.50	13.60	13.55	12.8	−0.75	33.2	0.39
205	76.25	185.0	24	13.40	13.65	13.50	14.1	+0.60	32.0	0.44
65	58.50	173.0	26	12.90	12.45	12.60	12.1	−0.50	28.5	0.42
7	73.50	181.0	43	13.35	13.45	13.40	13.1	−0.30	28.5	0.48
17	68.25	175.0	25	13.00	13.10	13.05	11.8	−1.25	30.4	0.39
12	79.50	186.5	23	13.60	13.80	13.70	12.8	−0.90	31.3	0.40
188	72.50	179.0	24	13.15	13.40	13.27	13.0	−0.29	29.0	0.45
196	61.25	163.0	19	12.40	12.60	12.50	12.1	−0.40	28.5	0.42
45	68.00	180.0	28	13.30	13.10	13.20	12.0	−1.20	28.8	0.42
185	69.00	174.0	28	12.95	13.15	13.05	12.4	−0.65	29.6	0.42
89	63.50	170.0	42	12.65	12.80	12.70	12.5	−0.20	28.5	0.48
120	69.00	181.0	34	13.35	13.15	13.25	13.2	−0.05	30.3	0.40
156	60.00	176.5	26	12.95	12.55	12.75	14.0	+1.25	30.0	0.46
50	59.50	163.5	29	12.45	12.50	12.50	12.7	+0.20	27.0	0.46
112	62.00	172.0	43	12.80	12.65	12.70	12.4	−0.30	27.6	0.45
213	71.00	169.0	30	12.70	13.30	13.00	14.1	+1.10	31.5	0.44
87	73.50	179.0	34	13.15	13.45	13.30	12.3	+1.00	30.5	0.40
71	71.50	176.0	21	13.00	13.35	13.17	13.3	+0.13	30.0	0.44
102	69.00	174.0	64	13.40	13.15	13.25	14.7	+1.45	28.0	0.52
212	67.50	176.0	22	12.95	13.05	13.00	12.2	+0.80	29.2	0.42
152	67.00	179.0	29	13.10	13.05	13.10	13.3	+0.10	31.5	0.42
28	68.00	180.0	23	13.30	13.01	13.20	10.2	−0.00	29.5	0.39
198	71.50	173.0	46	12.90	13.35	12.15	13.3	+1.15	29.3	0.45

* Diameter is expressed in centimeters.

The films of the extremities were studied to determine changes in the bones, soft tissues and vascular structures. The stereoscopic films were studied principally to note changes in the lung fields. The teleoroentgenograms were made in order to obtain data for comparison with standard measurements of normal individuals.

In studying the roentgenograms of the bony thorax, no abnormalities were noted except in 1 runner (No. 12) who showed a bifid rib; and in a second runner who had unusually slender ribs on one side (No. 102). The shadows of the upper mediastinum appeared to be normal. No changes in the pleura were observed except in 2 runners who showed obliteration of the costophrenic angle due apparently to some previous inflammatory reaction. The diaphragms, with one exception (No. 71), were smooth and regular in outline. So-called peribronchial markings were not increased and in some instances were actually less than would be expected in the essentially normal chest. One runner (No. 71) showed a moderate general increase in the markings of the lung fields similar to those noted in infections of the lower lobe.

Variations from the normal contour of the bony structures of the extremities were infrequent. Two runners showed unusual, bony proliferation on the dorsum of the tarsal scaphoid. One runner showed small localized thickening of the periosteum on the lower anterior aspect of the tibia. This change was the only instance of variation in the bones noted in 8 runners who had experienced so-called "shin-splints" during the race.*

Hypertrophic osteoarthritic changes of varying degree were noted in 6 instances. These occurred in the 5 runners over thirty-five years of age and in 1 runner (No. 152), aged twenty-nine years. The changes were minimal for the most part, consisting only of slight spur formations. One runner who had competed in long-distance events for forty years (No. 102), aged sixty-four years, had definite spurs on the lower thoracic vertebræ without the occurrence of symptoms. The bloodvessels were visualized in 5 athletes ranging from thirty-four to sixty-four years of age, the changes being confined to the lower extremities, except in 1 instance (runner No. 89) in whom the ulnar artery was also observed. The most striking density of the vessels occurred in the oldest runner (No. 102).

In the teleoroentgenographic studies, the greatest transverse diameter of the heart was measured for comparison with the tables of Bardeen.[6] The predicted diameter for each runner was computed for height and weight and an average obtained which was considered the normal diameter for the given individual. In the accompanying chart, it is noted that the actual transverse diameter fell below the predicted normal in 13 runners, the most striking instance was 1.24 cm. (No. 17), which was actually 10 per cent less than the

* An inflammatory condition of the muscles and adjoining tissues of the anterior tibial region.

predicted normal diameter. In the remaining 10 athletes, 5 showed variations of 1 to 1.45 cm. (Nos. 156, 213, 87, 102, 198), above the predicted transverse diameter; 5 runners appeared to have no striking increase in the size of the heart. In order to throw further light on the possible relationship between the size of the heart and the body, the so-called and commonly used cardiothoracic ratio[7] was employed. In normal people this ratio should not exceed 52 per cent. Only 1 runner, the oldest, No. 102, short, stocky in build, suggested an increase in the size of the heart.

In order to check the accuracy of the teleoroentgenograms, the cardiac shadows on the lung films were measured. These measurements showed a variation of only 2 mm. for 23 runners. The average size of the heart being approximately 1.5 per cent greater than in the teleoroentgenograms. In studying the lateral teleoroentgenograms, the cardiovertebral space appeared to be well preserved.

Comment. In considering the measurements of the heart it is realized that concentric hypertrophy, rotation of the heart and variations in the antero-posterior diameter may exist without being recognized by the teleoroentgenograms. The data, therefore, should be regarded critically. It appears, according to the standards of Bardeen,[6] that the hearts, as an average, were not increased in size since in only 5 instances were the cardiac shadows extended beyond the predicted normal. In view of the fact that 4 of this group were definitely underweight (3 to 4 kg.) and the fifth (No. 102) was short and stocky in build and aged sixty-four years, certain allowance for possible error may be considered in interpreting these measurements. The data derived from the so-called cardiothoracic ratio appear to strengthen the height-weight calculations. In this computation, the hearts were definitely within normal limits with the exception of runner No. 102, the same competitor, who, according to the tables of Bardeen, showed the most marked increase (1.3 cm.) in heart size. The normal appearance of the cardiovertebral space in all instances may be considered as evidence that no marked change occurred in heart size. The lung fields in comparison with the roentgenograms of the majority of normal city dwellers were unusually clear. This is interesting, perhaps, since the runners experienced unusual atmospheric conditions and had frequent upper respiratory infections.

In referring to the roentgenograms of the feet, it appears that the changes noted cannot be attributed to the act of running. This is striking when it is realized that improperly fitting shoes were used generally and difficult road conditions often traversed.

It is important, perhaps, to note that arteriosclerotic and osteoarthritic changes occurred in the older runners. This may suggest that disintegration of tissue is the penalty of age rather than of physical effort.

Conclusion. 1. A roentgenographic study of a group of long-distance runners was made to determine the effect of prolonged effort on the heart, lungs, bones and bloodvessels.

2. The lungs were found to be essentially normal.

3. The bones, except for certain osteoarthritic changes were normal.

4. The bloodvessels were visualized only in the older runners.

5. In 13 runners, the hearts appeared to be definitely smaller than normal, in 5 runners the hearts were within normal limits and in 5 instances the hearts, according to the predicted diameters, showed an increase in size. According to the so-called cardiothoracic ratio, only one heart was increased in size.

6. The data as a whole suggest that the immediate effects of long distance running are inconsequential, since all of the changes noted may be found in individuals of similar ages without symptoms.

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LIVER EXTRACT IN THE TREATMENT OF HYPERTENSION.

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Importance of the Hypertension Problem. An analysis of life-insurance statistics by Fisher[1] covering 2857 cases of hypertension shows that continued elevation of blood pressure definitely shortens life expectation, examples of long life in spite of a high blood pressure, notwithstanding. From Table I it can be seen that the shortening of life expectation is proportional to the degree of hyper-

tension, beginning with 114 deaths for every 100 expected deaths, according to the American Actuarial tables when the systolic pressure is 10 to 14 mm. above the average for any given age and reaching the enormous figure of 450 deaths for every 100 expected deaths in persons with systolic pressure of 60 mm. or more over the average for age. The average systolic pressure for age from a study of 36,104 normal cases[2] begins with 119 mm. for the quinquennium between fifteen and nineteen years, and gradually increases to 139 mm. for ages between sixty-five and sixty-nine years.

TABLE I.

	Per cent.
Percentage of expected deaths according to American Actuarial tables	100
Usual experience in accepted cases	86
10 to 14 mm. over average for age	114
15 to 24 mm. over average for age	181
25 to 34 mm. over average for age	205
35 to 44 mm. over average for age	246
45 to 59 mm. over average for age	254
60 plus mm. over average for age	450

Life expectation in persons with hypertension, from 2857 cases observed for periods of time up to eight years.

In order to elucidate the manner in which hypertension unfavorably influences the duration of life, subsequent impairments over a period of eight years in a group of 1274 people rejected solely for hypertension with an average systolic blood pressure of 159 mm. for the group are given in Table II. Fully 66.5 per cent of these impairments are referable to kidney damage and 17 per cent to degeneration of the cardiovascular system. To confirm this picture we have the fact that 83 per cent of applicants for life insurance presenting themselves with systolic pressure over 150 mm. can be rejected for albuminuria, hypertrophy of the heart, and so forth.[3]

TABLE II.

Impairment.	Number of cases.	Per cent.
Albumin in urine	120	
Albumin and casts	105	66.5
Casts	65	
Heart murmur	36	
Arteriosclerosis	29	17.0
Cardiac hypertrophy	9	
Nervous symptoms	21	
Sugar in urine	13	16.5
Miscellaneous	38	
Total	436	100.0

Impairments subsequently discovered or developed over periods up to eight years in 1274 cases rejected for high blood pressure only—ages forty to sixty years.
Average systolic blood pressure, 159 mm.
Mortality per cent for the group, 217 per cent.

Turning now to the causes of death in hypertension, it should be noted that Janeway[4] found in his series of 184 cases that about half of

the patients died a cardiac death, while apoplexy and uremia accounted for over a third of the deaths (Table III).

TABLE III.

	Per cent.	
Cardiac:		
Cardiac insufficiency	35.0	46.7
Angina pectoris	7.3	
Edema of lungs	4.4	
Uremic:		
Convulsions, coma, or gradual uremia		22.6
Cerebral:		
Apoplexy or its results		14.6

Percentages of the causes of death in 184 cases of hypertension in Janeway's series.

Finally, having statistically demonstrated the universally known close relationship between hypertension and cardiovascular-renal disease, it is well to keep in mind the important place which the latter occupies on the list of mortality statistics. For instance, an analysis of 17,500 deaths by the Northwestern Mutual Life Insurance Company[5] shows that 40 per cent were traceable to cardiovascular renal disease. This figure is probably too low because many of those who died on account of it are being reported as deaths from one of the forms of intercurrent infection.

The Question of Symptomatic Treatment in Hypertension. It is needless to say that the problem of etiology and mode of causation of hypertension is an extremely complicated one, which is as yet unsolved. All we can say at present is that it is a condition which may be caused by a variety of underlying causes. The question naturally arises as to whether we are justified in trying to reduce high blood pressure by means other than striking at the root of the trouble, of which hypertension is only a symptom. The answer to this question lies in the interpretation placed on the significance of hypertension. To quote from the excellent paper "High Blood Pressure from the Physiological Aspect" by MacWilliams:[6] "It may be looked on as a result of irritative and deranging influences (circulatory toxins or other causes) frequently leading to the development of symptoms of ill health, increasing the work of the heart and tending to cardiac failure, stressing the vascular walls, promoting their degeneration and predisposing to cerebral hemorrhage, kidney changes, etc. From another point of view, the high pressure may be looked on as essentially a compensatory process, while attended in the long run by certain unfavorable effects on the heart and bloodvessels. The raised pressure is regarded as compensatory in the sense of its maintaining the circulation or driving more blood through some vital organ that requires it—for instance, the brain, kidney, heart muscle, etc.—either when the flow has been subnormal or when a higher pressure and more rapid flow would be useful in view of functional or structural defects in the tissue."

As early as 1882, Conheim[7] suggested the compensatory theory of

high blood pressure and until recently the clinical evidence and opinions of clinicians were divided on this important question. Bier,[8] Janeway[9] and Clifford Allbutt[10] were defenders of this theory, while Mosenthal[11] opposed such an interpretation of hypertension.

During the last three years, much experimental work had been done on the question of the compensatory rôle played by high blood pressure, particularly in its relation to kidney function for which it was claimed to be especially advantageous. This view had in its favor the well-known regularity with which we see hypertension in certain types of nephritis. Reid,[12] in working on a group of hypertension cases, some with and some without renal impairment, was able to demonstrate that substantial prolonged lowering of high blood pressure (20 to 60 mm. for periods up to over a week), brought about by vasodilator drugs or by venesection, left the blood-urea and blood-nonprotein nitrogen levels unchanged. He also showed that reduction of hypertension in these cases did not change the total excretion of urea after administration of 15 gm. of this substance (MacLean test) and that the power of the kidneys to concentrate urea was commonly increased between 25 and 75 per cent, the largest fall in blood pressure giving the biggest increase in the power of concentration.

Regarding the excretion of chlorids, which is of interest, especially since F. Allen[13] ascribes such an important rôle to chlorid retention in the causation of hypertension, no comparable experiments have come to the attention of the writers but the following statement taken from de Wesselow's[14] work on "The Excretion of Chlorids by the Healthy and Diseased Kidney" is very suggestive: "Impairment of chlorid concentration is associated with a low response to the urea-concentration test. It may be concluded that both in interstitial nephritis and in various types of nephritis associated with edema the evidence suggests that impairment of the ability of the kidney to concentrate urea is associated with defective chlorid concentration, and that when one of these faculties is unaffected the other will be found to be intact."

Major[15] discovered increased guanidin elimination in 2 patients with hypertension during periods of induced lowering of the blood pressure.

Gruber, Shackleford and Ecklund[16] found that by lowering high blood pressure with phenobarbital the excretion of phenolsulphonephthalein was increased with the fall in blood pressure, but tended to decrease after prolonged administration of the drug, due probably to an increased rate of destruction of phenol derivatives after the tissues have been exposed to phenobarbital for a long time, because elimination again returned to its original level after withdrawal of the drug.

Finally, experiments by Dana,[17] Elliott,[18] Lawrence,[19] Mason[20] and Herringham[21] on hypertension cases, both with and without

renal damage, indicate that there is no definite relation between urinary output and lowering of the blood pressure induced by vasodilators. Reid[12] also found that water excretion was not changed by administration of drugs of the nitrite series when given in pharmacopeal doses. On the other hand, he states that diuresis after 15 gm. of urea was reduced in a majority of hypertension cases after administration of large amounts of vasodilators, but this may be due to the increased power to concentrate urea found in these cases. Moreover, some of his hypertension cases showed an actual increase in the urinary output under the above condition.

This series of experiments makes it evident that as far as we can tell, renal function is not impaired during periods of lessened blood pressure in hypertension cases, even in the presence of kidney damage.

Turning now to the heart, which next to the kidneys suffers from hypertension, and again quoting MacWilliams: "It is obvious that with declining heart power relaxation of the arterioles by vasodilator drugs would naturally produce unfavorable results, since the physiologic mechanism which tends to keep up the aortic pressure constriction in presence of defective cardiac output would be upset. But such considerations do not establish the beneficial or compensatory nature of the high pressures while the heart is efficient."

The desirability, from the standpoint of the heart, of lowering the blood pressure in hypertension is further emphasized by Fishberg's study[22] of the character and distribution of the arterial changes in cases of "essential hypertension," which brought out the fact that the arterioles in the heart muscle were only rarely involved, thereby confirming the theory that myocardial failure in hypertension is due mainly to overwork.

One more organ, namely, the brain, comes in for consideration when the possible compensatory rôle of hypertension is discussed. The immediate compensatory rise in blood pressure following experimental interference with the blood supply to the head, such as ligation of one carotid artery, and the findings of arteriosclerosis in the medulla of a number of hypertension cases by Bordley and Baker[23] make this a distinct possibility. On the clinical side, we have the frequency of cerebrovascular trouble beginning during sleep when the blood pressure is presumably at its lowest.

Without going into a detailed discussion of the above which would be outside the scope of the present paper, and for which the reader is referred to MacWilliams' paper, it should be mentioned that against the findings of Bordley and Baker we have those of Fisher showing even slight arteriosclerosis of the brain in only 20 per cent of his cases. While other observations prove that restless sleep is capable of producing much higher blood pressures than ordinary daytime activities, in one instance, a reading of 180 mm. systolic pressure on awakening was obtained in a man whose pressure during the day never exceeded 130 mm.

On the whole, it is felt by the authors that gradual reduction of blood pressure in hypertension cases under observation is justified and reasonably safe, especially because in case of any untoward symptoms due to fall in blood pressure the latter can be raised by administration of ephedrin with which one of the authors (T. L. A.) has had considerable experience.

Liver Extract. After the theoretical objections to lowering of high blood pressure were overcome in the light of the recent experimental work mentioned above, the practical difficulties in the way of prolonged reduction of hypertension still remained. All known measures affecting the blood pressure for any length of time until recently were of a more or less hygienic type, such as rest, weight reduction, dietary regulation, removal of foci of infection, and various types of physiotherapy, and their usefulness was largely limited to prevention. On the other hand, the effects of treatment by venesection and drugs of the nitrite series are only transitory and their prolonged application contraindicated for well-known reasons.

Since the work of Heidenhein,[24] in 1891, it was known that many organ extracts, and among others that of the liver, were capable of lowering the blood pressure in experimental animals. Limiting our attention to observers who investigated the depressor action of extracts of the liver, we find that Vincent and Sheen,[25] in 1903, produced in animals a fall in blood pressure with saline extracts of the liver. Bingel and Strauss,[26] in 1909, and Miller and Miller,[27] in 1911–1912, obtained the same results. Abel and Kubota,[28] in 1919, prepared a powerful depressor extract from the liver and attributed its action to histamin. Roger[29] in 1921–1922, obtained several different liver-extracts, one of which had a pressor and another one a depressor action. He was also the first one to suggest its therapeutic use in certain cardiac conditions.[30] Levin,[31] in 1922, gave to three diabetic patients hypodermic injections of dried liver and observed a fall in blood pressure.

Then, in 1925, Macdonald[32] working in coöperation with Lawton and James and Major[33] independently published the first encouraging results of liver-extract therapy of hypertension in human subjects.

Finally, Möller,[34] in 1927, working with liver extract prepared according to the Macdonald formula, reported 7 cases of hypertension treated for an average of thirty-two days, in whom reduction of high blood pressure caused no changes in the urinary findings, phenolsulphonephthalein excretion, blood urea, or per cent of hemoglobin.

The active ingredient of liver extract responsible for its depressor effect is unknown. Macdonald[35] in his extract found no protein or peptone but did find histamin in relatively small amounts (too small to account for its action) and cholin in relatively large quantities. The pharmacologic effects of his extract on arterial blood pressure, uterine muscle, intestinal strip and isolated heart, as well as its lethal effects when given in large doses, are identical with those of

histamin. Additional evidence in favor of histamin as the active component in liver extract is furnished by experiments of one of the present writers (T. C. B.)[36] with ducks in whom liver extract similarly to histamin can be injected without an appreciable effect on the blood pressure. Major[37,38] presented convincing animal experiments to show that the action of his extract was not due to peptone, cholin or histamin.

The liver extract used by us was prepared in the laboratory of Eli Lilly and Company, to whom we are indebted for the extract used

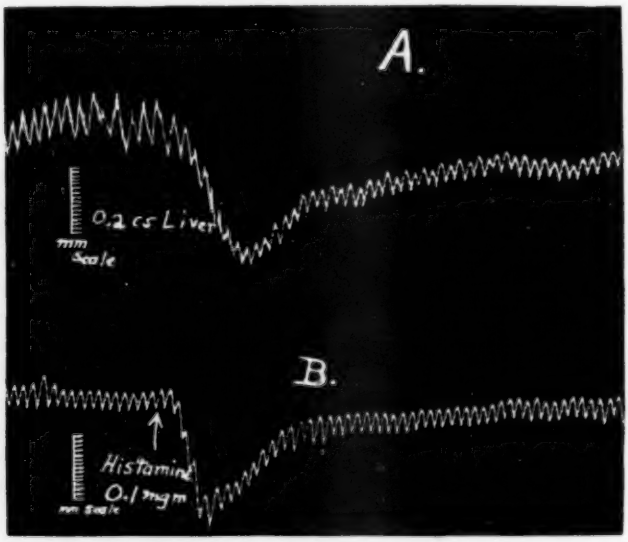

FIG. 1—Two blood-pressure curves taken on a dog (weight, 13.8 kilos): *A*, after injecting 0.2 cc. of liver extract. Initial pressure 150 mm.; *B*, after injecting 0.1 mg. histamin. Initial pressure 172 mm.*

in our study, under the name of "Heparmone" and is the result of collaboration by Macdonald, Major, Laughton and James. It contains no histamin, but a "histamin-like" substance and blood pressure in dogs is reduced by its action essentially in the same manner and for the same length of time as by the action of histamin. Fig. 1 shows comparative kymograph tracings of reduction in blood pressure produced by intravenous injection of 0.2 cc. of liver extract and of 0.1 mg. of histamin.[39]

The exact mechanism of the lowering of high blood pressure is still uncertain. However, it has been demonstrated[40] that liver extract acts independently of the vagus nerve and directly affects the bloodvessels, especially those in the splanchnic area. An inter-

* From paper by T. C. Burnett, The Depressor Action of Liver Extract. Am. Physiol., October, 1926, **78**, 449.

esting confirmation of this was brought to light when at autopsy on one of the refractory patients of Major,[33] intense arteriosclerosis of the splanchnic region was found. Experiments by James and Laughton[41] demonstrated that liver extract is capable of neutralizing the action of both adrenalin and pituitrin, thus indicating that it acts on arterioles when it prevents the action of adrenalin and on capillaries when it counteracts that of pituitrin. The latter finding is particularly significant in view of the possible bearing of the work of Krogh[42] and Richards[43] on the production of hypertension.

In regard to the therapeutic safety of the liver extract used by us in doses up to 5 cc. intramuscularly, it suffices to say that Miller and Martinez[44] have given over 200 cc. of it intraveneously in twenty four hours in cases of eclampsia without bad effects.

Selection and Examination of Patients. Our studies were carried on as much as possible in the out-patient department, where the patients could be kept under the usual conditions of work, diet, family environment, and so forth, thus eliminating the most important factor of uncertainty which enters into the appraisal of results obtained in the treatment of hypertension in hospitalized individuals. In all but 5 cases, the treatment was carried out entirely in the clinic. Moreover, two hospital cases in which reduction of blood pressure was produced were followed in the out-patient department. In the hospitalized patients, injections of liver extract were started only after the blood pressure had become stabilized in the new environment, the patients spending from four to twenty-seven days in bed (an average of thirteen days for our 5 cases) before the beginning of treatment.

At the beginning, in the light of the clinical results obtained by Macdonald[35] and Major,[33] an attempt was made to select a group of "essential hypertension" cases without cardiovascular-renal damage, but since practically every patient with hypertension had demonstrable involvement of one or both of the mentioned systems such a selection was abandoned and the cases taken consecutively.

In every case a complete history was taken and a general physical examination done with special attention to features indicative of functional or organic derangement of the kidneys, heart and blood-vessels.

The laboratory investigation included a complete analysis of urine, the phenolsulphonephthalein excretion test, the Mosenthal test, and the Wassermann test* in every case. In addition, blood urea and nonprotein-nitrogen determinations were done in 15 cases but later discontinued when a preliminary analysis disclosed that they had no bearing on the success or failure of liver-extract therapy.

Teleoroentgenograms of the heart and electrocardiograms were taken, as indicated.

* All reported cases proved to have a negative Wassermann reaction.

The majority of patients before receiving liver extract had gone through a period of treatment by dietetic measures (especially withdrawal of salt), and sedatives (mostly luminal) without much success except in 1 case in which a marked temporary fall in blood pressure was accomplished by a low-caloric, low-salt diet and absolute bed-rest.

Methods of Observation and Treatment with Liver Extract. The following method of taking blood pressures under as nearly constant conditions as possible was devised and strictly adhered to. All blood pressure estimations were carried out in the morning with the same sphygmomanometer applied to the right arm of patients who had rested in the prone position for at least ten minutes (usually about fifteen minutes). The ausculatory method was used. Every precaution against excitement was taken, syringes and needles were kept out of sight, no discussion of symptoms prior to taking the blood pressure was permitted, and so forth.

In determining the average blood pressure before treatment, at least several measurements were taken on different days and in the majority of cases the patients had been under observation for several months and often years prior to receiving liver extract. The average blood pressure following treatment was recorded for the entire period if the latter was less than one month and for the last month if it extended over several months, even if intermediate months showed a lower average.

The liver extract was always given intramuscularly into the arm with massage of the part following. The frequency of injections and the size of the dose were determined entirely by the response of the patient. A good scheme for the average case is to start with injections three times a week, beginning with 0.5 cc., then 1 cc., and so forth until at the end of two weeks 5 cc. are reached. By this time the value of the treatment in the individual case can usually be determined and in the successful case injections can be given once a week for a month, and then discontinued until the pressure begins to go up or until the patient will complain of a return of symptoms. The final dosage and frequency of administration is entirely individual. Often it is never necessary to go up to the higher doses or to give injections more than once a week from the very start.

No other treatment which would have any possible influence on blood pressure during the administration of liver extract was given to any of the patients whose records are discussed.

Results of Liver-extract Therapy. *Immediate Effects.* Following a single injection of liver extract there is in hypertension cases an immediate fall in the systolic and diastolic pressure lasting in our experience from two hours to a week. The degree of reduction of blood pressure is more or less in proportion to the dose in the same patient. As can be seen from Chart I, 0.5 cc. of liver extract lowered the blood pressure in Case XI by 15 mm. systolic and 11 mm.

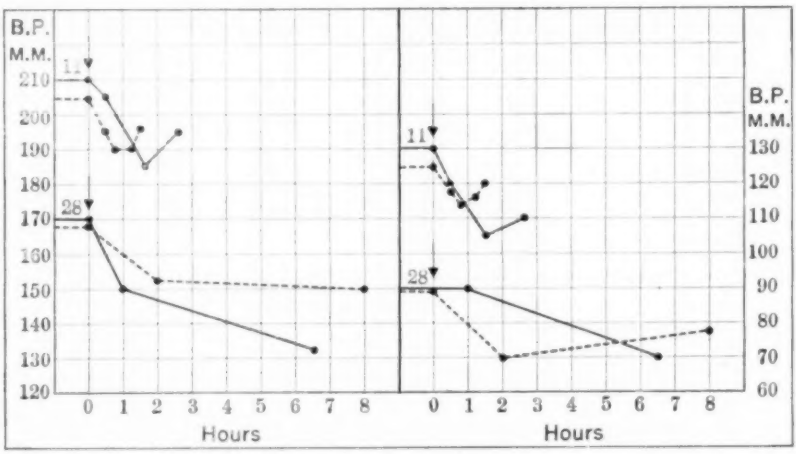

CHART I.—Chart showing immediate effects of liver extract on the systolic and diastolic blood pressure. The two upper curves show the effects of 0.5 cc. (broken line) and 1.5 cc. (unbroken line) of liver extract on the systolic (left) and diastolic (right) blood pressure of patient No. 11, who did not benefit from the treatment. The two lower curves show the influence of 0.5 cc. (broken line) and 1.0 cc. (unbroken line) of liver extract on the respective pressures of patient No. 28, who obtained a prolonged lowering of her blood pressure from the therapy. Arrows indicate when liver extract was given.

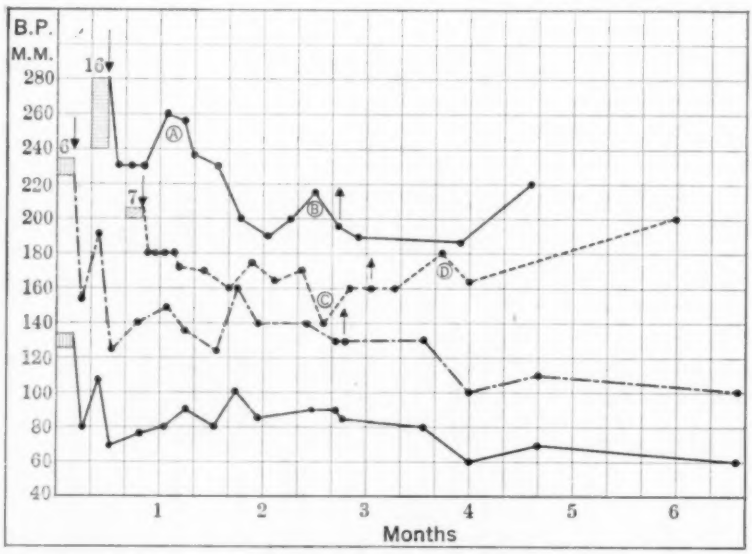

CHART II.—Chart showing prolonged lowering of the systolic pressure in 3 hypertension cases (Nos. 6, 7 and 16) whose blood pressure reacted favorably to liver-extract therapy. The diastolic pressure of Case No. 6 (lowest unbroken curve) is also shown as an example of how changes in the diastolic pressure usually correspond to those of the systolic. Rectangles indicate the range of fluctuations of the blood pressure prior to liver-extract injections. Arrows pointing down show the beginning of injections. Arrows pointing up indicate discontinuation of treatment.

A, patient had several attacks of gall-stone colic; *B*, patient's husband underwent an operation; *C*, patient had severe coryza; *D*, patient's car was stolen that morning.

TABLE IV.—CLINICAL DATA AND EFFECTS OF LIVER-EXTRACT THERAPY IN A GROUP OF HYPERTENSION CASES.

Case.	Sex.	Age.	Duration of hypertension.	Symptoms.	Physical findings.		Laboratory findings.						Blood-pressure.			Symptomatic relief.	Final dose, cc.	Duration of treatment, days.	Undesirable effects.	Previous treatment.	Remarks.
					Cardiac signs.	Vascular involvement.	Urine.		Mosenthal test.		Phthalein test.	Blood chemistry, mg. per 100 cc.	Average before treatment.	Average after treatment.	Average reduction.						
							Albumin.	Casts.	Nocturnal polyuria.	Fixation of sp. gr.											
1	F.	47	6 mos.	Headaches, dyspnea (marked), palpitation, hot flushes	Slight ankle edema; Ecg.? of myocardial damage and I.V. delay	None	F.T.	Many hyalin	+	0	70	Urea N. 16.8	180 105	160 103	20 2	Compl.	2	180	Local reactions	Low-salt, low-protein diet; limited fluids	After 0.5 cc. of liver extract blood pressure 165/100.
2	F.	62	1 mo.	Dyspnea, palpitation, tinnitus, fatigue	Slight ankle edema	Moderate arteriosclerosis	0	0	0	0	65	Urea N. 9.8	190 103	166 92	24 11	Partial	1	55	None	Allonal.	
3	M.	66	1 ¼ yrs.	Dizziness, tinnitus, sleeplessness, faintness, headaches	Slight cardiac enlargement	Moderate arteriosclerosis	S.T.	Many hyalin and granular	0	0	65	Urea N. 13.5	195 95	161 83	34 12	Marked	5	81	None	Luminal, potassium iodid, sodium bromid	After 0.5 cc. liver extract blood pressure 160/85.
4	M.	69	3 yrs.	Severe daily headaches, dyspnea, fatigue, blurring of vision	Cardiac enlargement; Roentgen ray aortic heart; systolic murmur at base	Marked arteriosclerosis; Roentgen ray aortitis	F.P.T.	Occ. hyalin and cellular	+	0	32.5	Urea N. 17.3	263 144	238 123	33 11	Marked	5	135	None	Low-salt, low-protein diet; allonal, citrin, pyramidon q. 4 hours.	
5	F.	48	1 yr.	Headaches, nervousness, fatigue, palpitation, dizziness	Slight cardiac enlargement	Moderate arteriosclerosis	0	0	0	0	80	Urea N. 20.1	220 115	199 103	22 12	Compl.	2	60	None	None.	
6	F.	61	6 mos.	Headaches, dyspnea	Ecg.? of myocardial damage	None	0	Rare granular	0	0	65	N.P.N. 33.7	230 130	105 65	125 65	Compl.	1	135	None	Low-salt, low-caloric diet; bed rest	After 0.5 cc. liver extract blood pressure 155/80.
7	M.	46	7 yrs.	Severe, constant headaches	Systolic murmur at apex	Moderate arteriosclerosis	0	0	+	0	30	Urea N. 11.7	203 113	159 97	44 16	Compl.	3	94	None	Luminal; adalin	After 0.5 cc. liver extract blood pressure 180/105.
8	F.	62	5 yrs.	Headaches, dyspneas	Slight ankle edema; systolic murmur at apex	Moderate arteriosclerosis	0	0	0	0	51	Urea N. 16.8	196 91	199 89	..	Partial	1.5	19	None	Low-salt diet; pyramidon.	
9	M.	51	6 mos.	Headaches, dizziness, blurring of vision	Moderate cardiac enlargement; systolic murmur at apex; Ecg. myocardial damage	Marked arteriosclerosis Roentgen ray sclerosis of arch	H.T.	Many hyalin	0	0	75	Urea N. 14	193 127	174 111	19 16	Marked	2	30	None	Low-salt diet, limited fluids; luminal, citrin, potassium iodid.	
10	M.	49	2 yrs.	Apoplexy 1 and 2 yrs. ago; fatigue	Systolic murmur at apex	Moderate arteriosclerosis	0	0	0	0	30	Urea N. 13.1	173 104	177 102	..	Marked	4	60	None	Low-salt, low-protein diet; luminal, potassium iodid.	
11	F.	50	15 yrs.	Headaches, dyspnea, palpitation; transitory blindness; hot flushes	Systolic murmur at apex; Ecg. S2 slightly slurred	Moderate arteriosclerosis	F.P.T.	0	0	7 pts.	70	Urea N. 16.8	194 110	191 113	..	None	2	14	None	Low-salt, low-protein diet; limited fluids; luminal	Hospital patient, rest in bed 4 days before treatment.
12	F.	48	2 yrs.	Occasional headaches; slight dyspnea; transient loss of consciousness and speech	Systolic murmur at apex; Ecg. myocardial damage	Moderate arteriosclerosis	F.T.	Rare hyalin	0	7 pts.	35	Urea N. 17.7 N.P.N. 28.6	180 110	169 108	11 2	None	1.5	11	None	Low-salt diet	Hospital patient, rest in bed for 27 days prior to treatment.
13	F.	59	3 yrs.	Headaches, dizziness, fatigue, nervousness, visual disturbance, speech difficulties, lapses of memory, numbness of extremities, right facial weakness	Slight cardiac enlargement; systolic murmur at apex; Ecg. myocardial damage	Moderate arteriosclerosis Roentgen ray aortitis	T.	Rare hyalin	0	5 pts.	32.5	Urea N. 21 N.P.N. 35.3	258 136	255 123	..	None	2	7	None	Low-salt diet; luminal; rest; potassium iodid; ovarian extract.	
14	F.	49	4 mos.	Severe daily headaches	Systolic murmur at base	Moderate arteriosclerosis	S.T.	0	+	6 pts.	55	N.P.N. 50	229 140	203 115	26 25	Marked	5	50	Transient urticaria	Low-salt diet.	

				nervousness, visual disturbance, speech difficulties, lapses of memory, numbness of extremities, right facial weakness	systolic murmur at apex; Ecg. myocardial damage	arteriosclerosis Roentgen ray aortitis		hyalin					N.P.N. 35	3	136	123		None	2	7	None	Low-salt diet; luminal; rest; potassium iodid; ovarian extract.	
14	F.	49	4 mos.	Severe daily headaches	Systolic murmur at base	Moderate arteriosclerosis	S.T.	0	+	6 pts.	55	N.P.N. 50	229 140	203 115	26 25	Marked	5	50	Transient urticaria	Low-salt diet.	
15	F.	41	3 yrs.	Severe headaches, nervousness, tinnitus, palpitation, dizziness, sleeplessness	Moderate cardiac enlargement	None	F.P.T.	0	+	4 pts.	50	...	218 130	188 114	30 16	Partial	2	14	None	Low-salt, low-caloric diet; luminal	After 0.5 cc. liver extract blood pressure 200/110.
16	F.	39	4 yrs.	Headaches, dyspnea, palpitation, dizziness, tinnitus, numbness of left half of body; precordial pain referred to left arm	Slight ankle edema; systolic murmur at apex; Ecg. right B.B. lesion	Moderate arteriosclerosis	H.T.	Occas. hyalin	0	0	30	...	260 153	198 117	62 35	Marked	5	90	None	Low-salt diet; luminal; ovarian extract	After 0.5 cc. liver extract blood pressure 230/130.
17	F.	50	3 yrs.	Constant headaches, nervousness, tinnitus, lapses of memory, difficulties in walking, inability to dress	Systolic murmur at apex	Marked arteriosclerosis	F.P.T.	0	0	0	30	...	190 106	193 102	..	Marked	4	37	None	None.	
18	M.	66	3 yrs.	Dyspnea, headaches, dizziness, paralysis of right leg	Systolic murmur at base	Marked arteriosclerosis	0	0	0	0	40	...	217 107	219 100	..	None	4	45	None	Low-salt diet; luminal; allonal; potassium iodid.	
19	F.	60	1 yr.	Dyspnea, palpitation, headaches	Slight cardiac enlargement; fibrillation controlled by quinidin; Ecg. myocardial damage	Moderate arteriosclerosis	0	0	0	6 pts.	40	...	183 112	170 99	13 13	None	5	39	None	Digitalis	Hospital patient; rest in bed for 9 days before treatment.
20	M.	65	13 yrs.	Dyspnea	Moderate ankle edema; moderate cardiac enlargement; loud A2	Moderate arteriosclerosis	0	0	0	5 pts.	65	...	201 93	179 67	22 26	Partial	5	33	Local reactions	Low-salt, low-protein diet; limited fluids; rest; cathartics	After 0.5 cc. liver extract blood pressure 180/70.
21	F.	28	2 yrs.	None	None	None	0	0	0	0	100	...	185 105	197 118	..	...	3	14	Local reactions	Low-salt diet.	
22	F.	38	5 yrs.	Dyspnea, headaches, nervousness, palpitation, dizziness, blurring of vision, precordial pain	Slight edema of ankles; slight cardiac enlargement, loud A2, systolic murmur at apex	Roentgen ray sclerosis of arch	0	0	0	7 pts.	70	...	250 139	215 106	35 33	Marked	5	47	None	None	After 0.5 cc. liver extract blood pressure 220/120.
23	M.	39	11 yrs.	None	Slight cardiac enlargement, loud A2	None	0	0	+	6 pts.	60	...	170 100	156 84	14 16	...	2	30	None	Low-salt diet; luminal	After 0.5 cc. liver extract blood pressure 155/85.
24	F.	53	4 yrs.	Headaches, palpitation, dizziness, dyspnea, precordial pain after heavy meals	Slight cardiac enlargement, systolic murmur at base; Ecg. right B.B. block; Roentgen ray, aortic heart	Moderate arteriosclerosis; Roentgen ray sclerosis of arch	S.T.	0	0	0	55	...	227 124	230 131	..	Marked	5	56	None	Luminal.	
25	M.	48	1 yr.	Headaches, dyspnea, palpitation, left hemiplegia	Slight ankle edema	Moderate arteriosclerosis	F.P.T.	0	0	0	55	...	175 116	169 112	..	Marked	3	24	Pruritus; local reactions	Luminal.	
26	F.	41	5 yrs.	Palpitation, tachycardia, precordial pain	Slight cardiac enlargement	Moderate arteriosclerosis; arteriovenous aneurysm	0	0	0	0	50	...	174 110	169 109	..	None	5	14	None	Rest	Hospital patient, rest in bed for 16 days before treatment.
27	F.	68	2 yrs.	Headaches, dyspnea, tinnitus, lapses of memory	Slight ankle edema; systolic murmur at base; diastolic murmur at base	Moderate arteriosclerosis	F.P.T.	Occas. granular	0	0	24	...	236 98	209 86	27 8	Partial	5	14	None	"Shots in arm"	Hospital patient, rest in bed for 9 days prior to treatment; after 0.5 cc. liver extract blood pressure 214/92.
28	F.	57	6½ yrs.	Headaches, palpitation, dyspnea	Slight cardiac enlargement; loud A2, systolic murmur at apex	Moderate arteriosclerosis	0	Few hyalin	0	0	50	Urea N. 8.4	180 90	168 84	12 6	Partial	1	5	None	Rest	Hospital patient, rest in bed 6 days before treatment.
29	M.	63	7 mos.	Dizziness, unsteady gait	Slight cardiac enlargement; loud A2, diastolic murmur at base	Marked arteriosclerosis	0	0	0	0	55	...	223 120	203 110	20 10	None	½	4	None	Luminal, citrin.	

diastolic, while 1.5 cc. reduced it by 25 mm. systolic and 25 mm. diastolic. In Case XXVIII 0.5 cc. and 1 cc. of liver extract on different days brought down the blood pressure 18 mm. systolic and 12 mm. diastolic and 38 mm. systolic and 20 mm. diastolic, respectively. The duration of reduction of blood-pressure is also to a certain degree dependent on the amount of liver extract given, as demonstrated by the fact that in Case XI the blood pressure curve after 0.5 cc. of it is already on the upward grade at a time when the reduction following 1.5 cc. is at its maximum. In addition, both the degree and duration of fall in blood pressure after single injections were more pronounced in patients in whom repeated liver-extract injections achieved a prolonged reduction of hypertension.

This is made clear by a comparison of the two curves in Chart I, of which the upper one belongs to a patient who failed to obtain lasting reduction in blood pressure or symptomatic relief from liver extract therapy, while the lower curve is from a case in which a more lasting fall of 12 mm. systolic and 6 mm. diastolic with partial relief of symptoms was produced. The curve of Case VI in Chart II shows a reduction of blood pressure lasting one week after the first dose of 0.5 cc. of liver extract.

Results of Repeated Injections. Besides the immediate, there is also in favorable cases, a delayed, more lasting reduction of hypertension following repeated injections of liver extract. This lasting reduction of hypertension which may, or may not, be accompanied by symptomatic improvement of the patient, is the main object of our interest. In Chart II are given blood-pressure curves from 3 cases which responded to liver-extract therapy. Altogether liver extract was given in 29 cases of hypertension and a summary of the important individual clinical findings will be found in Table IV. Only 27 of our cases were used for analysis of the results of treatment, because in view of the natural course of hypertension it was felt that before any conclusions can be drawn cases showing reduction in blood pressure must be followed for a longer period of time than it was possible in the 2 last cases. The average time of treatment with liver extract in cases which responded by lowering of the blood pressure or with symptomatic improvement, or both, was a little over two months. On the other hand, the average time during which injections were given to patients who failed to respond in either of these two ways was eighteen days.

1. Reduction of the average systolic blood pressure of 10 mm. or more took place in 17 out of 27 cases, or in 63 per cent of all cases.

The average reduction of systolic pressure in these cases was 32.7 mm. and the greatest average fall of the systolic pressure in any 1 case was 125 mm. (from 230 mm. to 105 mm.). Lowering of the diastolic pressure was generally in proportion to that of the systolic. The average reduction of the diastolic pressure in these 17 cases was 18.9 mm., while the most marked average fall for any case was 65 mm. (130 mm. to 65 mm.).

The greatest single fall in blood pressure was observed in Case VI, amounting to a reduction of 75 mm. in systolic and 50 mm. in diastolic pressure in two days without any untoward symptoms.

2. Symptomatic relief was obtained in 19 out of 25 patients who complained of symptoms referable to hypertension, or in 76 per cent of all cases. Of these 5 (or 20 per cent) were completely relieved; 9 (or 36 per cent) were markedly relieved; 5 (or 20 per cent) were only partially relieved; 6 or (24 per cent) were unchanged. The symptoms complained of in order of their frequency and those that were completely or markedly improved, are given in Table V. The

TABLE V.

Symptoms.	No. of cases.	Per cent. of all cases.	No. of cases improved.	Per cent of cases improved.
Headaches	19	70	13	80
Dyspnea	15	56	7	47
Dizziness	11	41	7	64
Palpitation	11	41	6	55
Edema of legs	8	30	6	75
Tinnitus	6	22	3	50
Visual disturbances	5	18	3	60
Fatigue	5	18	2	40
Nervousness	4	15	3	75
Precordial pain	4	15	3	75
Impairment of memory	3	11	1	33
Insomnia	2	8	1	50
Numbness of extremities	2	8	1	50
Unsteadiness of gait	2	8	1	50
Speech disturbances	2	8	0	0
Vasomotor instability (hot flushes)	2	8	0	0

Tabulation of symptoms associated with hypertension in our series and those completely or markedly relieved by liver-extract therapy.

symptoms most complained of were: Headaches, dyspnea, dizziness, palpitation and edema of the ankles. The ones relieved most readily were: Headaches, edema of the ankles, nervousness, precordial pain and dizziness. Speech disturbances, impairment of memory, fatigue and dyspnea were the most refractive symptoms. It is interesting to note that only 2 of our patients (both of them women) had hot flushes, probably of a menopausal character, which were unrelieved by treatment. Partially relieved symptoms were left out of this table on account of a desire to deal only with definite improvement and if possible to discount the psychic effect that any treatment may produce. In this connection, attention is again called to the fact that all but 3 of the patients in this series had had previous treatment without much success.

The remarkable symptomatic relief achieved in some of our cases can be illustrated by Cases IV and XVII selected from at least half a dozen similar ones. Case IV had very severe continuous headaches for over a year, for which he was in the habit of taking about every four hours pyramidon or similar analgesic drugs with slight relief. In addition, he suffered from dyspnea, fatigue and

blurring of vision. After one week of liver-extract therapy he stopped all other medication and was having on the average only about one slight headache a week, and also reported great improvement in his other symptoms.

Case XVII, who was brought to the clinic, unable to dress or to walk without assistance and in addition had constant headaches, tinnitus, extreme nervousness and lapses of memory, improved under treatment to such an extent that she was comfortable and able to take care of herself when last seen.

Discussion. It soon was noticed that a fall in blood pressure was not always accompanied by relief of symptoms, and that at times very marked subjective improvement followed liver-extract therapy without any lowering of blood pressure. In this series 2 cases of the first type and 5 cases of the second category are included. Moreover the degree of subjective improvement in many cases appeared unrelated to the amount of lowering of the blood pressure.

For this reason in an effort to determine the type or types of hypertension cases suitable for liver extract our successes and failures to lower the blood pressure or to give symptomatic relief are analyzed separately from the standpoint of age, sex, degree and duration of hypertension, kidney involvement, cardiovascular damage, and dosage of liver extract.

Age in our cases, as seen from Table VI, had apparently no connection whatever with the outcome of treatment, for the average age of patients whose hypertension was decreased proved to be about the same as the age of those whose blood pressure remained unaffected. The same is true of the group that obtained and the one that failed to obtain symptomatic relief. As a matter of fact, the youngest patient treated was twenty-eight years of age and a failure, and the oldest sixty-nine years of age and a success.

TABLE VI.

Group of patients.	Average age.	Sex.		Average blood pressure before treatment, mm.		Duration of hypertension, years.
		Males.	Females.	Systolic.	Diastolic.	
Blood pressure reduced 10 mm. or more . . .	52.8	6	11	212	118	3.25
Blood pressure unchanged	50.6	3	7	199	111	4.35
Symptomatic relief obtained	53.3	7	12	212	117	3.00
No symptomatic relief .	54.0	1	5	201	114	4.80

Influence of age, sex, height of blood pressure and duration of hypertension on the results of treatment with liver extract.

Sex also exercised no demonstrable influence on the success or failure of liver-extract therapy.

In our series there were twice as many women as men and this proportion was found to be maintained to a surprising degree for such a small number of cases in all groups except the one that obtained no symptomatic relief in which there are 5 women and only 1 man. This is against the current opinion that often menopause in females brings about a more tractable type of hypertension than that found in men. Our findings in this respect confirm Alvarez's[45] contention that hypertension is a bodily peculiarity inherent equally in both sexes but "ordinarily repressed in women before the menopause by the ovarian or other related secretions." Apparently, when once liberated from this repression it behaves in no way differently from hypertension in men.

The degree of hypertension, somewhat to our surprise, did not prove to be of any prognostic significance as far as results with liver-extract treatment are concerned. On the contrary, the average systolic pressure (Table VI) in patients whose blood pressure was reduced and in those who obtained symptomatic relief was 13 mm. and 11 mm. respectively, higher than in the two failure groups. These findings would be in accord with the known fact that in the natural course of hypertension a spontaneous fall of the systolic blood pressure due to cardiac exhaustion late in the disease takes place, and would admit of the interpretation that the two failure groups are composed of more advanced cases. But such an explanation can hardly be valid in the face of a corresponding lower diastolic pressure in the two latter groups, amounting to 7 mm. and 3 mm. respectively, while we know that the diastolic pressure is not lowered and even may be raised after myocardial failure sets in. Moreover, such a small difference in the average blood pressure in those two groups would have to be true for a much larger number of cases to be really significant.

Duration of hypertension as calculated from the time of discovery by sphygmomanometric measurements appears to have a very definite influence on the outcome of liver-extract administration. The average duration of hypertension in cases in which the diastolic blood pressure was reduced over 10 mm. as a result of treatment is 3.25 years, while in the group that failed to obtain a fall in blood pressure it is 4.25 years or one-third (33 per cent) greater. It is interesting to note that if we compare the average duration of hypertension in patients in whom the blood pressure came down 15 mm. or more with that of the group in which the reduction was less than 15 mm. or none, the relative difference becomes doubled (64 per cent), the respective figures being 2.8 years and 4.6 years.

Of even greater significance is the duration of hypertension as a determining factor in symptomatic relief. Namely, its average duration in cases which were improved is three years while in patients who did not, it is 4.8 years or more than one-half (60 per cent) greater. This finding is even more striking if we compare the

average duration of hypertension according to the degree of relief afforded. In cases with complete relief it is 1.8 years, in cases of marked relief 2.5 years, and in cases with only partial relief 4.6 years.

Bearing of Kidney Involvement on Results of Treatment. In view of the divergent opinions held as to the part played by kidney impairment in the production of hypertension, special attention was paid to a complete functional investigation of kidney activity with the object of determining the relationship, if any, between different types of impairment of renal function and the results of treatment with liver extract.

To begin with, only 4 patients in our series were free of demonstrable kidney involvement, and these 4 patients did not respond in a uniform way to liver extract. The results of the various kidney tests are given below in correlation with success or failure of treatment for hypertension.

Urinary Findings. It is of interest that in our series a negative urine was found in a somewhat greater percentage of cases which failed to show reduction in blood pressure (50 per cent) than in those that did (35 per cent) (Table VII). Of the individual abnormal constituents albumin was found with about equal frequency in both groups, but casts were found five times as often in the group that responded by lowering of the blood pressure. Casts occur when there are active degenerative changes in the tubular epithelium and this in conjunction with the shorter duration of hypertension in the favorable group may indicate an earlier stage of nephritis which, later when there is more interstitial fibrosis, gives less evidence in the urinary findings in spite of a greater real damage to the kidneys in the unfavorable cases.

On the contrary, the urinary findings were of no significance as far as the symptomatic relief afforded by the treatment is concerned; as can be readily observed from Table VII.

Phenolsulphonephthalein Excretion Test. The ability of liver extract to reduce hypertension does not appear to be influenced by the power of the kidneys to excrete the dye, as shown by the average phthalein excretion for the two groups in Table VII. The same is more or less true in regard to subjective improvement, though here the successful group shows a slightly higher 'phthalein excretion (50.9 per cent *versus* 44.6 per cent) and this is most marked in the patients who obtained complete relief with an average output of 61.2 per cent. On the other hand, there are marked individual exceptions in all groups so that much significance cannot be attached to these averages.

Blood-urea Nitrogen and Total Nonprotein-nitrogen Determinations. Early in our work blood chemistry investigations on the fasting stomach were carried out on every patient, but later they were discontinued when a preliminary analysis of data showed that these had no bearing on the results of liver-extract therapy. Altogether

TABLE VII.

Group of patients.	Urinary findings.						Average phenolsulphonephthalein excretion, per cent.	Average blood-urea nitrogen level, mg. per 100 cc.	Mosenthal test.			
	Albumin.		Casts.		Negative.				Nocturnal polyuria.		Fixation of specific gravity.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.			Cases.	Per cent.	Cases.	Per cent.
Blood pressure reduced 10 mm. or more	10	59	8	47	6	35	53.6	15.1	6	35.0	6	35.0
Blood pressure unchanged	5	50	1	10	5	50	51.4	16.9	..	..	2	20.0
Symptomatic relief obtained	11	58	7	37	7	37	50.9	14.8	5	26.3	3	15.8
No symptomatic relief	4	67	2	33	2	33	44.6	18.5	..	..	4	67.0

Bearing of kidney involvement in hypertension on the success of liver-extract therapy.

TABLE VIII.

Group of patients.	Degree of cardiac involvement.						Arteriosclerosis.						Average final dose of liver extract.
	Marked.		Moderate.		None.		Marked.		Moderate.		None.		
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	
Blood pressure reduced 10 mm. or more	6	35.0	7	41.0	4	23.5	2	11.7	10	58.8	5	29.4	3.26
Blood pressure unchanged	2	20.0	3	30.0	5	50.0	4	40.0	5	50.0	1	10.0	3.35
Symptomatic relief obtained	6	31.5	7	36.8	6	31.5	4	21.0	10	52.6	5	26.3	3.44
No symptomatic relief	2	33.3	3	50.0	1	16.6	2	33.3	4	66.6	..	..	3.25

Results of liver-extract treatment of hypertension in the light of cardiovascular damage and dosage of liver extract.

15 patients were thus investigated and with one possible exception no abnormally high nitrogen levels were noted. Moreover, the relative differences in nitrogen levels were only so slightly in favor of the two successful groups that one cannot speak even of a less prompt excretion of nitrogenous products in cases where treatment failed in one way or another.

Mosenthal Test. The most interesting and consistent findings on the relation of kidney function to liver-extract therapy were obtained from this test.

In the first place, nocturnal polyuria was found exclusively in the two groups that responded to treatment, about one-third of the patients in whom the blood pressure was reduced and one-fourth of the patients with symptomatic relief exhibiting it. In other words, over half of the patients in these groups (50 and 55 per cent respectively, to be exact) showing any impairment to the Mosenthal test had nocturnal polyuria. This is very remarkable in face of the fact that it was found in none of the patients failing to respond to treatment.

In the second place, fixation of specific gravity was in a striking manner found most commonly in patients who obtained no symptomatic relief. As against those who did, this finding was four times more prevalent in the former group (67 against 15.8 per cent). On the other hand, no such decisive effect could be observed in the matter of blood-pressure reduction.

The most probable explanation of these phenomena is that all our patients showing abnormalities in the Mosenthal test are affected by vascular nephritis, but in various degrees. Nocturnal polyuria, which is the first sign of excessive irritability of the renal vessels and is found in mild forms of vascular nephritis, is met with in early stages of hypertension, which naturally yield better to therapeutic measures. Conversely, fixation of specific gravity is encountered in more severe forms of vascular nephritis found in patients whose hypertension is of longer duration, and therefore, is discovered more often in patients who obtain no relief from treatment. This explanation is also entirely supported by the already discussed fact that the shorter the duration of hypertension previous to liver-extract therapy, the better the results.

Results of Treatment in the Light of Cardiovascular Damage. Organic disease of the heart and bloodvessels is so closely related in the patient with hypertension, and criteria of quantitative involvement of each are so difficult to establish that only a rough distinction between "marked" and "moderate" involvement of either is attempted below.

Cardiac Damage. The facts on which the amount of cardiac impairment was judged are given in Table IV. From a percentage analysis of the cardiac involvement in the four groups (Table VIII) it is clear that twice as many patients were free from demonstrable

cardiac damage in the two failure groups as in the two successful groups, and that a correspondingly greater number of patients who benefited by the treatment showed involvement of the heart. It seems difficult to interpret these findings unless it can be assumed that a heart with less reserve can be more easily made to drop part of its load and that some of the relief experienced by patients in this group can be ascribed to such lessened demand on their cardiac muscle. Whatever the explanation, it seems clear that organic lesions of the heart constitute no contraindication to liver-extract therapy.

Arteriosclerosis. Evidence regarding arteriosclerosis was obtained by palpation of the accessible arteries, by ophthalmoscopic examination, and by roentgenologic evidence in reference to calcification in the aorta.

A glance at Table VIII is sufficient to show that hardening of the arteries and its degree, if present, are of great importance in predicting the outcome of treatment. None of the patients without arteriosclerosis failed to get symptomatic relief and only in one such patient did the blood pressure fail to come down. Conversely, marked arteriosclerosis was found to be more prevalent in the two failure groups. This unfavorable influence of arteriosclerosis is especially marked in relation to lowering of the blood pressure as can be seen from the fact that a marked degree of it was found almost four times more commonly in patients whose blood pressure did not react favorably to liver-extract injections.

Relation between Dosage of Liver Extract and Success of Treatment. The maximum single dose of liver extract given to patients before the treatment was pronounced a failure was smaller in early cases than in later cases. In this connection the question arose as to whether this factor could have impaired the validity of our conclusions by segregating in the successful groups the patients who received larger doses. To answer this question the largest doses of liver extract given in each case were averaged in the four groups and were found to vary only between 3.25 cc. and 3.44 cc. in the two extreme groups. Differences in the number of injections and the total amount of liver extract received could be of no such significance because obviously the treatment was kept up only in cases which benefited from it. On the other hand, it cannot be denied that better results might have been produced in a few of our early cases if larger doses of liver extract had been employed at the time.

It is of theoretical interest and of practical importance that in 10 out of the 17 cases in which hypertension was lowered by 10 mm. or more, the first injection of 0.5 cc. of liver-extract produced a substantial lowering of the blood pressure when taken under constant conditions two days later and compared with the average level previous to treatment.

The average reduction of blood pressure after the first injection of

liver extract in the 10 cases that definitely showed it was 28 mm. for the systolic pressure and 18 mm. for the diastolic pressure. The average total fall in these cases after prolonged treatment was 41 and 23 mm. for the respective pressures. The symptomatic response in these patients was not appreciably different from that in the whole series. The practical significance of this finding lies in the fact that in 60 per cent of our cases in which a substantial lowering of the blood pressure was produced the success of liver extract therapy could have been predicted after the first injection of a small dose. Moreover, the remaining 40 per cent which required larger doses in order to affect their blood pressure showed only half as great a total fall in blood pressure, amounting to 19 mm. systolic and 10 mm. diastolic for the group.

On the basis of the above, it is felt by the authors that the apparent higher percentage of effectiveness of liver extract in this series as compared to the averaged reports received by Eli Lilly and Company[46] on all cases treated with heparmone up to seven months ago, which was 52 per cent, is simply a matter of dosage. Their recommendation to us was to inject between 0.2 cc. and 0.6 cc. of liver extract a day, but owing to our facilities of supervision over patients we in all probability went farther in the matter of increasing this dosage when advisable than most physicians using the Lilly liver extract.

While it is true that some patients with hypertension, who are not affected by small doses of liver extract, respond to larger ones, and that in those who do, larger doses will produce a greater effect, there is no strictly quantitative relationship between the dose of liver extract and the degree of prolonged lowering of high blood pressure. In other words, a patient in whom a marked reduction of hypertension has taken place after small doses of liver extract, say 0.5 cc., will not get much more of a fall in blood pressure after ten times this dose, even if his blood pressure is still considerably above normal.

The explanation for this peculiarity which places liver extract in a different class from such organ extracts as insulin, thyroid extract, parathormone, and so forth is not known, but whether we are permitted to draw an analogy between its action and that of vitamins, is an open question.

In taking a hint from Major's[38] work with dogs in which he was able to reduce the artificially raised blood pressure with small amounts of liver extract, while even very large doses did not lower the normal blood pressure, the following considerations explaining the action of liver extract in the reduction of hypertension, seem justifiable: In a sufficiently large series of consecutive hypertension cases the patient will fall in three main groups. At one extreme there will be cases in which all bodily functions can be carried out satisfactorily under conditions of normal blood pressure. In between there will be gradations of cases which we can call for convenience

"hypercompensated" in which some elevation of blood pressure is necessary for adequate function, but who carry blood pressures in excess of the required minimum increase. The etiologic and time relationships of these cases do not interest us for the present. If such a series be treated with liver extract, in some cases the blood pressure will come down to normal, in others it will be reduced in varying degrees down to the minimum necessary for proper function, in some it will remain unchanged, and in some it will creep upward in spite of treatment, all depending on whether there are underlying processes which create a real need for an increased blood pressure. In relation to practical therapeutics, this means that we need not be afraid to cause, by the use of liver extract a dangerous fall in blood pressure in an unsuitable case, or by overdosage in a suitable one, because the blood pressure simply will not come down below the individual level of safety in each case, unless shock doses are used.

What the underlying processes of true compensatory hypertension are remains for the future to show, but even from our small series we can form some idea as to their nature, by focusing attention on consistent abnormalities found in patients who did not respond to treatment. Such consistent abnormalities, as already stated above, are sclerosis of vessels and the more advanced stages of vascular nephritis. It is a subject for reflection that just these changes will eventually develop secondary to so-called "essential hypertension" of long standing.

Undesirable Effects of Liver Extract. Undesirable effects of liver-extract therapy in hypertension could be expected from lowering of blood pressure and from local or systemic toxic effects of the preparation.

No untoward symptoms from any part of the body, referable to reduction of hypertension, were observed in any of our cases, not even a temporary discomfort from this cause during the period of adjustment was reported, though the fall in blood pressure in some cases was very considerable, amounting up to 75 mm. in two days, and up to 125 mm. during the course of treatment.

Local reactions at the site of injection, consisting of redness, swelling and a circumscribed feeling of heat lasting about two days took place in 4 of our patients after several injections were given. Reactions never occurred after the first injection. The second injection after onset of such reactions usually gave the greatest discomfort and after four injections followed by reactions the latter ceased to appear. The local effect at the site of injection during this period of susceptibility was the same, no matter which arm was used. In no case were these reactions of sufficient severity to contraindicate further treatment.

General reactions, such as described by Macdonald[32] and also by Möller,[34] as consisting of a chill, high fever, backache, malaise, a feeling of nervousness, and a great transient fall in blood pressure were never seen in our patients. The reason for this probably lies in

the recent development of more refined methods used in the preparation of the extract.

Möller in a recent paper also described the appearance of urticaria in one, and itching erythema in 2 out of his 10 cases following liver-extract administration. In all 3 cases the lesions lasted for two days. Going back over our records, we find that 1 patient developed a transient attack of urticaria while under treatment, and another patient developed considerable pruritus after twenty-four days of liver-extract therapy. Whether these cutaneous manifestations are due to liver extract we do not know.

Duration of the Effects of Liver Extract following Repeated Injections and the Question of Tolerance. In 8 successful cases which were under liver-extract treatment for periods of time varying from twenty-five days to six months with an average of two months for all cases, the injections were discontinued and the patients observed at weekly intervals for rise of blood pressure and return of symptoms. In two of these patients, a definite rise in blood pressure took place at the end of four and five weeks respectively, and 1 patient had a return of his headaches at the end of a month.

The remaining 5 patients at the present writing retained the full benefits of their treatment; 2 for one month, 1 for five weeks, 1 for six weeks, and 1 for two and a half months.

The only possible indication of an acquired tolerance to liver extract was observed in Case I. This patient's blood pressure was reduced and kept at the upper limits of normal for four months with 1 cc. injections of liver extract given from two to three times a month. After four months weekly injections of 2 cc. were required to accomplish the same result. It is realized that one such case has very little significance except to direct attention to this phase of liver-extract therapy, and that it can be very well explained by the natural course of the disease.

The gradual diminution in local reactions, when these occur, does not constitute evidence in favor of tolerance to the preparation. These local reactions, in our experience, never take place after the first injection of liver extract, but only after repeated injections, so that their occurrence must be credited to sensitization and the gradual disappearance to desensitization rather than to initial susceptibility and acquired tolerance.

Value of Liver-extract Therapy. The value of liver-extract therapy in hypertension at present is two-fold. From the patient's point of view, it is justified in favorable cases on account of symptomatic relief, which in such cases is unequalled by any therapeutic procedure known heretofore. In cases which respond by lowering of blood pressure, it also serves to take off, or at least to diminish, the extra load imposed on the heart by hypertension. In this way, secondary cardiovascular renal degenerative changes probably can be prevented or their progress slowed down.

From the point of view of the investigator, the most important

objective of liver-extract therapy is to keep the blood pressure down in a sufficiently large number of hypertension cases for a sufficient length of time to determine whether, even without the high blood pressure, the familiary organic changes of the hypertensive syndrome will appear in cases where they are absent, or whether such changes will progress in cases where some of them are already present. The answer to this will decide once for all the long controversy as to whether an "essential" elevation of the blood pressure or minute organic changes constitutes the primary evil of the disease under consideration.

Hypertension among University Students. The most decisive answer to the stated problem would be furnished by treating, as mentioned above, hypertension cases without any evidence of cardiovascular-renal impairment. Unfortunately, we failed to find a sufficient number of such cases in the out-patient department. Remembering the work of Alvarez,[47] who reported that during routine physical examination of freshmen entering the University of California 20 per cent of 2930 men had a systolic blood pressure over 140 mm.* and 12 per cent of 5807 women showed a systolic blood pressure over 130 mm.,* we turned our attention to this field.

With the coöperation of Dr. Cunningham, Dr. Schultz was able to follow up at the University of California Infirmary 17 out of 24 women freshmen who, at their entrance examination in January, 1928, had blood pressures of 140 mm. or over. According to Alvarez's paper, such blood pressures which were found only in 2.4 per cent of women students could be definitely expected to have a pathologic significance. To our surprise, repeated blood-pressure estimations on these students after five minutes' rest in the reclining position showed normal readings between 98 and 132 systolic in 13 cases. Of the remaining 4 cases, 2 had frank nephritis and 2 had grossly infected tonsils, for which tonsillectomy was advised with a good prospect that this operation will bring the blood pressure down to normal, as has been observed many times at the Infirmary.

The importance of the observation that all 13 cases of hypertension in students for which no definite cause could be found showed a normal blood pressure after a few minutes of rest is still enhanced by the fact that 8 of these cases had blood pressures over 145 mm. (found only in 0.8 per cent of women students in Alvarez's series) and that in 6 cases it exceeded 150 mm. (reported only in 0.4 per cent of cases in the same series).

In consequence we again failed to assemble a group of so-called "essential hypertension" cases for liver-extract therapy and became even more convinced of the rarity of this syndrome, provided that it exists in reality at all.

The significance of transient hypertension under emotional stress, such as a medical examination cannot be stated at present. It is

* Alvarez accepted this as the upper limit of normal for this sex.

possible that individuals subject to it are marked for permanent hypertension in later life, or that the whole thing may be based on vasomotor instability. The latter interpretation is suggested by an interesting experience with one of the students whose blood pressure when taken immediately after entering the examiner's office was 154 mm. systolic and 90 mm. diastolic, but after five minutes' rest came down to 98 mm. systolic and 70 mm. diastolic.

The Use of Liver Extract for Purposes other than Treatment of Hypertension. The number of accidental discoveries of effective therapeutic agents is so large that it behooves clinical investigators to fully explore even remote possibilities of new applications for physiologically potent substances in our possession.

In line with this thought, Miller and Martinez[44] tried the effect of liver extract in eclampsia and reported favorable results.

At the University of California Hospital, liver extract was tried in a case of uremia with anuria and in 1 case of arteriovenous aneurysm. The first patient, a young woman with severe diffuse nephritis and marked hypertension of at least one and a half years' duration, fell into a rapidly progressing uremia and after four days of increasing oliguria became anuric. On the third day of her anuria and the day before death, she was given 1 cc. of liver extract intramuscularly and twenty minutes later voided 90 cc. of urine without change in her blood pressure.

The other case, one of spontaneous aneurysm of undertermined etiology between the left carotid artery and the cavernous sinus in a middle-aged woman who had suffered from moderate hypertension for five years, was treated with liver extract in an endeavor to promote the formation of a thrombus by lowering the blood pressure. The attempt was abandoned after eight injections of liver extract amounting to a total of 25.5 cc. reduced her systolic blood pressure by only 5 mm. and failed to produce any evidence of thrombosis.

Summary. 1. *Introduction.* (*a*) The importance of the hypertension problem in connection with high mortality due to cardiovascular-renal disease is pointed out. (*b*) Symptomatic treatment of hypertension at the present incomplete stage of our knowledge as to its etiology is justified. (*c*) A brief historical and pharmacologic survey of liver extract is given.

2. *Methods of Liver-extract Therapy.* (*a*) The selection and examination of patients is mentioned. (*b*) The procedures used in observation of patients and administration of liver extract are outlined.

3. *Results of Treatment with Liver Extract.* (*a*) The immediate effect of a single injection of liver extract in hypertension cases is to produce a fall in the systolic and diastolic blood pressure. The extent and duration of this fall are within limits in proportion to the dose in the same patient, but vary greatly from case to case. (*b*) After repeated injections of liver extract in 27 consecutive cases of hypertension it was found that in 17 cases, or 63 per cent of all cases,

a reduction of the average systolic pressure of 10 mm. or over took place. The average reduction of systolic pressure in these cases was 32.7 mm. The diastolic pressure in the same cases was reduced by an average of 18.9 mm. (*c*) Out of 25 patients who had symptoms referable to hypertension, definite relief was obtained by liver-extract therapy in 19 cases or 76 per cent of all cases. Headache was the most common complaint and marked or complete relief from it was reported in 80 per cent of cases that had it.

4. *Analysis of Findings.* The fact that reduction of hypertension and symptomatic relief did not always go together prompted a separate analysis of the factors making for success or failure of liver-extract therapy from these two points of view.

Age, sex and the degree of hypertension proved to be immaterial in determining the success of liver-extract therapy. On the other hand, the duration of hypertension prior to treatment was found to affect very markedly the prognosis of therapy inasmuch as patients who did not obtain reduction in blood pressure on symptomatic relief were known to have had high blood pressure much longer than those who did.

The urinary findings and the various kidney function tests were found to have unequal bearing on success of liver-extract therapy: Casts were found five times more often in the group that responded by lowering of the blood pressure. The phenolsulphonephthalein excretion test proved of no important prognostic significance in treatment with liver extract, but on the whole, high dye excretion was favorable for symptomatic relief. Blood-nitrogen determinations were in no way helpful in the present treatment of hypertension. The Mosenthal test proved to be of great significance inasmuch as nocturnal polyuria was found exclusively in the two groups that responded to treatment while fixation of specific gravity was four times more prevalent in patients who obtained no symptomatic relief than in those who did.

The presence or amount of cardiac damage was of no significance, as far as success of the treatment was concerned. Arteriosclerosis and its degree, if present, were of great importance in predicting the outcome of treatment since none of the patients without arteriosclerosis failed to get symptomatic relief and only in 1 such patient did the blood pressure remain elevated. Conversely, marked arteriosclerosis was found to influence the outcome of the treatment unfavorably, especially in relation to lowering of the blood pressure.

The success or failure of the treatment cannot be ascribed to the size of the dose since the average final dose in all four groups was practically the same. It was observed that the first dose of liver extract produced a substantial lowering of the blood pressure in 60 per cent of our successful cases, and that these cases subsequently showed the greatest prolonged reduction of their blood pressure.

5. *Undesirable Effects of Liver Extract.* No undesirable symptoms referable to reduction of hypertension were observed in any case.

In 4 cases, temporary mild local reactions were observed which must be ascribed to sensitization.

6. *Duration of the Effects of Liver Extract following Repeated Injections and the Question of Tolerance.* In 8 successful cases of liver-extract therapy the effect of the treatment extended over periods of between one month and two and a half months, after the injections were discontinued. No definite evidence of an acquired tolerance to the drug was noticed.

7. *The Use of Liver Extract for Purposes other than Treatment of Hypertension.* A patient with anuria on a uremic basis voided after an injection of liver extract. Efforts to induce thrombosis of an arteriovenous aneurysm by lowering the blood pressure with liver extract were unsuccessful.

Conclusions. 1. The treatment of hypertension with liver extract brings about a considerable lowering of the blood pressure and affords complete or marked symptomatic relief in a majority of cases.

2. Hypertension cases of known duration under two years, without marked arteriosclerosis, and showing no fixation of specific gravity in the Mosenthal test, offer the best prognosis.

3. The most important objective of the present work from the point of view of the investigator is to determine by observations over a long period of time whether cardiovascular-renal damage can be arrested or prevented by artificial lowering of high blood pressure in hypertension.

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HIGH-CARBOHYDRATE DIETS IN DIABETES MELLITUS.

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Since the realization that over 50 per cent of protein is converted, in the body, into carbohydrate, our main reliance for calories for the diabetic has been on fat. Before this time, protein seemed the obvious food, as fat produced acid and carbohydrate sugar. The use of high-fat diet was furthered by a more definite knowledge of the ketogenic-antiketogenic ratio, by which we were able to give fat and carbohydrate in proportions that obviate the difficulty of acid-body formation. Newburg and Marsh[1] carried the use of fat to its most extreme point, giving an amount of fat that was beyond what we usually had considered desirable according to the ketogenic-antiketogenic ratio. These amounts of fat are often much greater than are found in the customary diet of the normal individual, and if one examines carefully the stools of patients fed in this way, a considerable amount of unabsorbed fat and fatty acid are often found. There has been an increasing suggestion in the literature of diabetes that these high-fat diets, even though they give calories by mouth, are not well absorbed or borne by the body. We cannot always demonstrate an acidosis, and yet we know that the patient does not feel as well as he should. Allen[2] has pointed out that fat has a definite influence on the amount of insulin necessary, and Greenwald, Gross and Samet[3] suggest that fat has a definite influence to lower glucose tolerance. Others have confirmed these findings.

Before the time of insulin, it was not possible to avoid this condition because, only in our mild cases, could we give sufficient carbohydrate to be of practical value in combating the acidosis. At present, there is no bar to our giving as large an amount of carbohydrate in twenty-four hours as we wish, and increasing the insulin accordingly.

Sansum[4] has for several years strongly advocated this procedure. He gives a diet which contains practically a normal amount of starch, as much as 300 gm. or more of carbohydrate per day, and to take care of this, gives as much as 200 units of insulin in twenty-four hours.

At the University Hospital Metabolic Clinic, we have been attempting for some time past to ascertain just how far we could raise the carbohydrate of the diet, especially if we cut the fat to a much smaller proportion than that generally used. We did this with several objects in view: (1) From a practical standpoint it seemed likely that patients on a large carbohydrate intake would be

more faithful in their adherence to the prescribed diet. (2) Furthermore, we wished to see whether our patients would feel better on a diet of more carbohydrate and less fat. (3) We thought that there might be a more or less definitely balanced ratio between the fat and the carbohydrate which could be metabolized by the body.

It is quite evident that both carbohydrate and fat have a definite influence on the use of insulin by the body. This is true whether the insulin is the natural insulin of the pancreas or the extracted product. Carbohydrate seems to use insulin for its own metabolization, but whether fat also uses insulin for this purpose, or whether it in some way inhibits the use of the insulin by the carbohydrate we do not know. Joslin[5] has pointed out repeatedly the influence that body fat has in the etiology of diabetes, and it is common observation that increased body fat in a diabetic lowers the tolerance for carbohydrate in the diet. It is also well known that keeping a constant carbohydrate in the diet of the diabetic, and raising the fat, will sooner or later bring sugar into the urine.

It has been suggested that this influence of the fat is so great that it is possible to transpose the number of grams of fat and carbohydrate in a satisfactory diet, and still have the patient remain sugar-free. Our experience in the clinic definitely justifies this statement. We have approached this attempt to give higher carbohydrate in two ways. In some patients we have definitely transposed the number of grams of carbohydrate and of fat in a maintenance diet, and have observed whether the patient remained sugar-free and continued a normal blood sugar. In others we have departed from these definite figures, trying to see how high we could go with the carbohydrate if we cut the fat to a correspondingly low level. These we have done in both our insulin patients and in those whose cases are too mild to require insulin. Sixty-one patients have been treated in this way with satisfactory results in all of the patients, except those who were greatly overweight.

Clinical Notes. The following cases demonstrate the results of this changing of fat and carbohydrate:

CASE I.—L. B., male, aged thirty-four years, weight 130 to 135 pounds. March 30 to November 22, 1926, the diet was: Carbohydrate, 57 gm.; protein, 58 gm.; fat, 150 gm., with insulin 32 units A.M., and 14 units P.M., urine sugar, negative; blood sugar, normal and no insulin reactions. On November 22, the diet was changed to: Carbohydrate, 150 gm.; protein, 58 gm.; fat, 57 gm., and the same amount of insulin prescribed. On his next visit, December 28, his urine was sugar-free and has remained so with this diet and insulin until the present. On June 13, 1928, his fasting blood sugar was 0.113 per cent.

CASE II.—C. C., male, aged thirty-two years, weight, 127 to 132 pounds, is an electrician. On January 7, 1927, the diet was: Carbohydrate, 51 gm.; protein, 56 gm.; fat, 104 gm., with insulin 40 units A.M.; urine sugar-free, blood sugar normal and no insulin reactions. On January 7, the diet was

changed to: Carbohydrate, 104 gm.; protein, 56 gm.; fat, 50 gm., with same insulin. On the next visit, February 4, his urine was sugar-free and has remained so until the present. On June 12, 1928, his fasting blood sugar was 0.120 per cent.

CASE III.—B. S., male, aged nineteen years, weight 155 to 160 pounds, was on a high-carbohydrate diet in the clinic for two years. He was then hospitalized for infection and was discharged with a diet of: Carbohydrate, 100 gm.; protein, 65 gm.; fat, 150 gm. This was later changed to: Carbohydrate, 77 gm.; protein, 65 gm.; fat, 169 gm., with 35 units insulin A.M., 25 units P.M., and on this he remained for five months, during which time his urine was sugar-free, he had normal blood sugar and no insulin reactions. On April 20, 1928, the diet was transposed, making it: Carbohydrate, 169 gm.; protein, 65 gm.; fat, 77 gm., and the same insulin was prescribed. On the next visit, May 18, his urine was sugar-free, and he has continued with this diet and insulin until the present. On June 8, his fasting blood sugar was 0.075 per cent.

CASE IV.—J. F., male, aged thirty years, weight 125 to 130 pounds, was for several years on a low diet, namely: Carbohydrate, 50 gm.; protein, 56 gm.; fat, 100 gm., with insulin 40 units A.M., 30 units noon 30 units P.M., urine sugar-free, normal blood sugar, and no insulin reactions. On June 24, 1927, the diet was transposed to: Carbohydrate, 100 gm.; protein, 56 gm.; fat, 50 gm., with the same insulin. On the next visit, July 1, the patient's urine was sugar-free and has continued so until the present on the same diet and insulin; on June 8, 1928, the fasting blood sugar was 0.119 per cent.

CASE V.—R. M., male, aged thirty-eight years, weight, 135 to 140 pounds, had been on a diet of: Carbohydrate, 100 gm.; protein, 60 gm.; fat, 200 gm. with 16 units insulin A.M. for several months, and had had negative urine, normal blood sugar and no insulin reactions. On August 2, 1926, the diet was changed to: Carbohydrate, 200 gm.; protein, 60 gm.; fat, 100 gm. with the same insulin. On the next visit, September 23, the patient's urine was sugar-free and has continued so on the same diet and insulin until the present. On June 18, 1928, the fasting blood sugar was 0.131 per cent.

CASE VI.—A. H., female, aged forty-seven years, weight, 140 to 145 pounds, had a gradually increasing chronic nephritis with a blood-urea nitrogen from 25 to 35 mg. per 100 cc. of blood. The diet on March 21, 1927, was: Carbohydrate, 100 gm.; protein, 56 gm.; fat, 150 gm., insulin 10 units A.M., 5 units P.M., urine sugar-free, fasting blood sugar 0.132 per cent, no insulin reactions. Diet was changed to: Carbohydrate, 130 gm.; protein, 50 gm.; fat, 130 gm., with the same insulin. On her next visit, June 29, the patient's urine was sugar-free on this diet and insulin, and continued so, with a fasting blood sugar of 0.111 per cent on August 5. On this date the diet was changed to: Carbohydrate, 175 gm.; protein, 40 gm.; fat, 100 gm. with the same insulin. The patient returned on March 16, 1928, urine sugar-free. On May 28, the fasting blood sugar was 0.131 per cent.

CASE VII.—R. H., female, aged fifty years, weight, 115 to 120 pounds, on May 13, 1927, was on a diet of: Carbohydrate, 77 gm.; protein, 58 gm.; fat, 156 gm., with 25 units insulin A.M., 15 units P.M., urine sugar-free, normal blood sugar and no insulin reactions. On this date, the diet was changed to: Carbohydrate, 156 gm.; protein, 58 gm.; fat, 77 gm. with the same amount of insulin. On the next visit, May 27, 1928, the patient's urine was sugar-free and she had a normal blood sugar. The patient remained so until October, when infection intervened.

It is evident from these figures that we have kept our patients on as low a number of calories as is consistent with maintaining strength and weight. The latter we try to keep at 10 per cent less than the standard weight for height, age and sex. Of course we realize that, as we cannot supervise our patients' diet at home, they may be taking more food than we prescribe. However, with careful checking by the dietitians, using all of the methods which they know to discover deviations from the diet, we think that any extra amount taken is not likely to be large.

We feel that if the patients maintain their weight and strength, as criteria of good nourishment, that the number of calories given per day is not of great importance. The maintenance of weight especially is apparently carried on as well with carbohydrate as with fat, in spite of the decreased number of calories, in some cases, even better. In addition to the cases already referred to, the following are of interest.

CASE VIII.—E. W., female, aged nineteen years, weight, 100 to 105 pounds, during the winter and spring of 1926 was on a diet of: Carbohydrate, 60 gm.; protein, 55 gm.; fat, 120 gm. with 30 units of insulin A.M. and 18 units P.M., with occasional lapses from either or both. On July 19, 1928, after being sugar-free on this diet and insulin for several months, she weighed 103½ pounds. On this date the diet was changed to: Carbohydrate, 120 gm.; protein, 55 gm.; fat, 60 gm. with the same insulin. On August 2, 1926 the patient's urine was sugar-free on the new diet, and she weighed 109 pounds. On September 10 her urine was still sugar-free and she weighed 110 pounds. The patient continued sugar-free and with a weight of 108 to 110 pounds until December, when disregard of diet caused acidosis.

CASE IX.—L. S., female, aged sixteen years, weight, 128 to 134 pounds, was referred from the hospital ward on diet of: Carbohydrate, 65 gm.; protein, 56 gm.; fat, 125 gm. On March 1, 1927 she was on this diet with 25 units insulin A.M., 15 units P.M. and her urine was sugar-free. On this date the diet was changed to: Carbohydrate, 125 gm.; protein, 56 gm.; fat, 65 gm., with the same insulin. On April 13 her urine was sugar-free and she weighed 136 pounds on this diet and insulin. On May 18 her urine was sugar-free and she weighed 143 pounds.

On the other hand, it has been evident that with patients who are fat or markedly overweight it is not possible to make this change in the fat and carbohydrate of the diet. The tolerance has been exceeded and sugar in the urine has resulted in all of those cases which we have tried. There is apparently present in these patients the influence of the body fat, which makes it impossible for the body to take advantage of the reduction of the fat in the diet. We have found one patient, not overweight, who was not able, with several attempts, to make this change in his diet without showing sugar in the urine.

We feel that the ability of patients to metabolize more carbohydrate cannot be due to increased tolerance for food. Such increase

in tolerance as would account for these cases takes a considerable time to develop, while these changes in the diet were made at one time, and examinations of the urine and blood were made at frequent intervals. No time was allowed for development of a greater tolerance.

The patients were also on the highest diet which they could take with the given amount of insulin, as shown by blood sugars and by the fact that when the diet was increased, sugar appeared in the urine. In the insulin patients this is also evident because if the insulin had been sufficient to allow for a marked increase in carbohydrates, it would have been sufficient to cause shock during the period of the low-carbohydrate, high-fat diet.

In addition to demonstrating that the change in carbohydrate and fat can be made, the patients have shown two definite advantages from the change. They have, without exception, commented to us in the clinic on how much better they have felt on a high-carbohydrate diet. They could not readily describe the physical discomfort which seemed to result from a high-fat diet, but they knew very well that they did not have this discomfort when their diet was changed. Also, it has been clear to us that the patients more nearly stayed on their prescribed diets. The increase in carbohydrate is often enough to allow them a small amount of bread or potato, thus helping to satisfy their craving for starch. This has been a great help to us in preparing diets as well as to the patients themselves. It has been our observation that patients often desire starch more than they do sweets, and these amounts of carbohydrate give them a most satisfying diet.

Conclusions. Attention has been called to the fact that if we reduce fat in the diet, the carbohydrate can be greatly increased in many patients without their showing sugar in the urine or having an increased blood sugar. Resulting from this diet, there is a greater feeling of well-being in the patients and a greater ease in keeping them on the prescribed diets because of the increased carbohydrate allowance.

NOTE.—I wish to acknowledge the coöperation and assistance of Miss Ruth Wilkinson, Dietitian of the University Hospital.

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REVIEWS.

EPILEPSY. By WILLIAM G. LENNOX, Research Fellow in Neuropathology, Harvard Medical School, and STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School. Pp. 197; 14 illustrations. Baltimore: The Williams & Wilkins Company, 1928. Price, $3.50.

THIS limited study is "the presentation of evidence which may throw light on the mechanism involved in seizures, and on the cause and treatment."

Theories as to the neurologic mechanism involved are: irritation, release, short circuit, and explosive which perhaps is the most plausible.

Conjecture as to the fundamental element in the precipitation of the seizure is "oxygen lack."

Luminal is the most useful drug. Fat-feeding, and magnesium sulphate as a dehydration agent, may prove helpful.

N. Y.

A TEXTBOOK OF SURGERY. By W. WAYNE BABCOCK, M.D., F.A.C.S., Professor of Surgery and of Clinical Surgery in the Temple University, Philadelphia; Surgeon to the Samaritan Hospital and to the American Hospital for Diseases of the Stomach. Pp. 1367; 1050 illustrations, 9 of them in colors. Philadelphia and London: W. B. Saunders Company, 1928. Price, $10.00.

THIS first edition has already reached, if it has not exceeded, the ultimate limit in size of a textbook. It may still be said that in general it covers the field systematically, clearly and briefly. The sections on Treatment are definite and contain many hints born of practical experience. Illustrations are copious and well chosen. Especially valuable to the student are those freely supplied with legends to illustrate important points in pathology or treatment. The practising surgeon will find the book a useful compend of a veritable system. In a book frankly dedicated to the presentation of a cross section of present-day surgical practice, one might question the prominence given to such operations as gastroplication, cecopexy, operation for incompetent ileocecal valve, peritoneo-

saphenous anastomosis and the author's operations of vaginal enterostomy and telescopic anastomosis of the stomach and intestine. The book is avowedly and necessarily somewhat dogmatic and posseses a strong personal flavor. While this always has both advantages and disadvantages, it is fair to say that this book is a valuable contribution and there are few indeed who will not find in it much of interest and help. The publishers have done their part well. D. P.

CILIARY MOVEMENT. By J. GRAY, M.A., Fellow of King's College and Lecturer in Experimental Zoölogy in the University of Cambridge. Pp. 162; 105 illustrations. New York: The Macmillan Company, 1928.

IN addition to its general scientific interest as one of the most primitive types of activity of animal cells, ciliary movement has a practical medical importance in connection with various problems involving the respiratory tract, the Fallopian tubes, and so forth. A volume such as the present one by one of the foremost living students of cilia is therefore doubly welcome. Among the subjects considered by the author are: The general character of ciliary movement, the force exerted and the work done by cilia, the relation of ciliary movement to ionic equilibria and the metabolism of ciliated cells. M. J.

THE OPIUM PROBLEM. BY CHARLES E. TERRY, M.D., AND MILDRED PELLENS. Pp. 1042. New York: Committee on Drug Addictions in Collaboration with the Bureau of Social Hygiene, Inc., 1928.

THIS book embodies studies conducted for the Committee on Drug Addictions to reveal the status of knowledge of the various aspects of the problem of opium addition. In it are abstracts of or extracts from more than 600 publications, classified under the headings: Extent and Development of the Problem; Etiology and General Nature of Addiction; Somatic and Psychic Changes; Tolerance, Dependence and Withdrawal; Symptomatology; Treatment; Control. The terms of the Hague Opium Convention and of the acts of the Geneva Conferences of the League of Nations are appended together with the text of the U. S. Narcotic Laws. The work appears to have been competently done, but the reader who approaches this book with the hope of finding any of the important questions connected with opium decided for him will be disappointed. In large measure the compilers have refrained from comment other than that required to make the extracts clearly intelligible. What

the book does is to show vividly the state of confusion of present knowledge and opinion. It should serve as a valuable source book and as a strong stimulus to research for physiologists, physicians or students of society. The contents of the book are well indexed.

E. K.

BIOLOGICAL CHEMISTRY AND PHYSICS OF SEA WATER. By H. W. HARVEY, M.A., Hydrographer at the Laboratory of the Marine Biological Association, Plymouth. Pp. 194; 65 illustrations. Cambridge: The University Press, 1928. Price, 10 s., 6 d.

IN recent years there has been a greatly increased interest in many quarters in oceanographic problems. The present timely volume gives a useful collection of data on such subjects as the chemical constitution of sea water, the tides and currents of the sea, oceanic temperatures and the chemical and physical factors controlling the density of population of marine organisms. A bibliography at the end of each chapter adds greatly to the usefulness of the book.

M. J.

LES ASSOCIATIONS MICROBIENNES LEURS APPLICATIONS THÉRAPEUTIQUES. By G. PAPACOSTAS and J. GATÉ. Pp. 431. Paris: Gaston Doin et Cie, 1928. Price, about 75 cents.

THIS small, inconspicuous and inexpensive book broaches some interesting aspects of bacteriology that receive scant or no treatment in the conventional textbooks. Symbiosis and parasitism of vegetables, animals and bacteria are first discussed in a general way, then specific examples of microbic mutual stimulation and antibiosis *in vitro* and *in vivo*. To one who has had, for instance, to search the literature for examples of antagonism in disease, this is a very useful book; to all, it should be stimulating and interesting.

E. K.

A TEXTBOOK OF PATHOLOGY. By WILLIAM G. MACCALLUM, M.D., Professor of Pathology and Bacteriology, Johns Hopkins University. Fourth edition. Pp. 1177; 606 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price, $10.00.

THE regular quadrennial appearance of this book seems to indicate that we need a new MacCallum's *Pathology* about as often as a new president. Comparison with the first edition (1920) shows that, while arrangement and subdivision of subjects is essentially the same, skill has been used in keeping the book up to date with

the addition of only 86 new pages. In the process, "general pathology" has suffered somewhat, also such borderline topics as immunity, acid-base equilibrium, cardiac arrhythmias, which though possessing true pathologic aspects are necessarily or by convention fully treated elsewhere. The extra space gained is devoted mostly to tuberculosis (15 pages), syphilis (18 pages) and other infections (29 pages), the blood-making organs (19 pages) and tumors (13 pages). Yellow fever, dengue, deficiency diseases and others find places not accorded them in the first edition.

Emphasis properly continues to be laid on the author's "own autopsy experience and changes in attitude." In spite of the fact that the subject arrangement is quite different from the conventional order of treatment in medical schools (or perhaps partly because of it), the book remains the most satisfactory of any for students' reading. The detailed table of contents and index preserve its value as a book of reference. E. K.

THE TRUTH ABOUT MIND CURE. By WILLIAM S. SADLER, M.D., F.A.C.S., Senior Attending Surgeon to Columbus Hospital; Director of the Chicago Institute of Research and Diagnosis. Pp. 206. Chicago: A. C. McClurg & Co., 1928. Price, $2.00.

THIS writer has delivered many lectures and has written many books, so he admits. And while the present volume does not deal completely with modern mind cure, its insufficiencies may be met by the perusal of other books by the author.

"Mind cure is nothing more nor less than faith cure."

The mastery of the "nerves" and the liberation of one's self from the bondage of despair is best achieved through "a good job, a good fad and a good religion."

Though not a scientific treatise, here is found some wholesome advice for family use, in language that is clear and concise.

N. Y.

A LABORATORY MANUAL OF PHYSIOLOGICAL CHEMISTRY. By D. WRIGHT WILSON, Department of Physiological Chemistry, School of Medicine, University of Pennsylvania. Pp. 272. Baltimore: Williams & Wilkins Company, 1928. Price, $3.50.

THIS manual is a revision of one used by the author over a number of years in teaching classes in physiological chemistry of medical and dental students, and contains ample laboratory material for an extended course in general physiological chemistry. The experiments are accompanied by considerable discussion of the fundamental principles involved, particularly in the section on electrolytic

dissociation and its applications, and no pains have been spared to acquaint the student with those modern fundamentals, a knowledge of which is so urgently needed by the present-day student of medical chemistry.

A large share of the material presented is quantitative in nature. As a handbook of quantitative methods, particularly on urine and blood, it should find wide use. A section of animal experiments on dietary deficiencies has been included as has also a four-place logarithm table and a table of 1928 atomic weights. Alternate pages have usually been left blank to permit the recording of notes by the student. W. G. K.

CRITERIA FOR THE CLASSIFICATION AND DIAGNOSIS OF HEART DISEASE. By a COMMITTEE appointed by the HEART COMMITTEE OF THE NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION, INC., consisting of JOSEPH H. BAINTON, M.D., ROBERT L. LEVY, M.D., W. C. MUNLY, M.D., M.C., U. S. A., and HAROLD E. B. PARDEE, M.D. Pp. 92. New York: Paul B. Hoeber, Inc., 1928. Price, $1.50.

THIS little book contains a classification of heart disease according to the nomenclature first adopted by the New York Heart Association in 1923 and with certain changes later adopted by the American Heart Association. There have been added what are regarded as the definite criteria for these diagnoses. The classification used has worked out very successfully and might well be adopted not only by cardiac clinics but by hospitals generally. The criteria given enhance the value of the classification. The book may properly be regarded as representative of the best thought in cardiology and should be in the hands of all interested in the subject. C. W.

PHYSICAL DIAGNOSIS. By CHARLES PHILLIPS EMERSON, A.B., M.D., Professor of Medicine, Indiana University School of Medicine; author of *Clinical Diagnosis*. Pp. 533; 324 illustrations. Philadelphia and London: J. B. Lippincott Company, 1928. Price, $7.00.

THE author states that "Physical diagnosis needs adequate emphasis in these days of laboratory diagnosis and instruments of precision," and again: "Textbooks on physical diagnosis usually treat of but few organs, especially the lungs and heart. This limitation, however, is unreasonable . . ."—(opinions in which the Reviewer heartily concurs). In an attempt to cover the whole field of physical diagnosis, he has accordingly produced a book which for its size contains an enormous amount of information. The style is vivid and interesting and there is a profusion of illustrations,

for the most part very good. Numerous footnote references to original sources facilitate further study.

Certain minor criticisms are indicated. In an attempt to cover so broad a field, the work at times becomes unduly shallow and superficial, a defect that is only to be overcome by greater length. There have been omissions, some of them intentional, which may not generally be considered justified. For instance, cardiac arrhythmias are illustrated only by pulse tracings; there are no electrocardiograms and no diagrammatic illustrations, without which the average student might have considerable difficulty in grasping the subject. There is no reference to the physical signs of foreign body in the lower air passages, to inanition edema, to tongue appearance in diabetes and sprue, to the difference of level and motion of the two sides of the diaphragm when the patient is lying on his side. Right-sided hydrothorax in heart failure is wrongly attributed to pressure by the dilated *left* auricle on the right lung hilum. There is an undue number of misspelled words, for example, Stensen (Stenson), Einthofon (Einthoven), Lennec (Laennec), Klumple (Klumpke); terygium, malasikterus, cardology and so forth. Many of the illustrations of skin lesions were from the collection of the late Dr. Milton B. (not S.) Hartzell. However, as aforesaid, these are minor criticisms and readily to be corrected in new editions of which it is hoped the work will experience many. Practitioners and students will find here much to further "the seeing eye, the hearing ear and the understanding fingers." R. K.

AN INTRODUCTION TO EXPERIMENTAL PHARMACOLOGY. By TORALD SOLLMANN, M.D., Professor of Pharmacology and Materia Medica at Western Reserve University, Cleveland, Ohio, and PAUL J. HANZLIK, M.D., Professor of Pharmacology at Stanford University, San Francisco. Pp. 321; 39 illustrations. Philadelphia and London: W. B. Saunders Company, 1928. Price, $4.25.

THIS book embodies the extensive experience of one of the most distinguished teachers of pharmacology in the United States (Sollmann), amplified by that of his pupil, Hanzlik. In the form of concise directions for a systematic course it describes a great variety of experiments on the medical characteristics and actions of most of the drugs which the medical student must learn. The impression is given that nothing has been omitted which is susceptible of successful demonstration to or by students. Its literature references, descriptions of technique and tables of dosage for animal experiments make it invaluable to a teacher of pharmacology or of physiology; the student who uses it as a guide will not only learn pharmacology at first hand, but will also obtain splendid training in the experimental method. A. R.

DISEASES OF THE BLOOD. By A. PINEY, M.D., M.R.C.P., Research Pathologist, Cancer Hospital, London. Pp. 195; 20 illustrations. Philadelphia: P. Blakiston's Son & Co., 1928. Price, $4.00.

MANY small books on the anemias, diseases of the blood, and so forth, have appeared in the past few years, but the author of this one feels that still another is justified as it presents not too much hematologic detail for the student and only "bare outlines of immediate practical value" for the practitioner—truly negative reasons for presenting material in but little greater detail than one would find in the usual textbook of medicine at a cost almost half that of the larger book. The customary topics are treated in a sound manner, as one would expect from one of the author's standing. An occasional anglicism such as "large hyaline leucocyte" for "large mononuclear" or "monocyte" fails to injure the easy flow of the author's pleasant style. "Acute leukosis" serves for "acute leukæmia," "leukæmic myelosis" for "myeloid leukæmia," and so on. The illustrations are well drawn, though some of the colored ones have suffered in reproduction. One regrets a total absence of references. E. K.

BOOKS RECEIVED.

NEW BOOKS.

Treatment of Venereal Disease in General Practice. By E. T. BURKE, D.S.O., M.B., CH.B. (GLAS.). Pp. 162; 8 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $1.75.

Method of Biological Assay. By J. H. BURN, M.A., M.D. (CAMB.) Pp. 126; 22 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $3.55.

Lipiodal in the Diagnosis of Thoracic Disease. By F. G. CHANDLER, M.A., M.D., (CANTAB.) M.R.C.P. (LOND.) and W. BURTON WOOD, M.A., M.D., (CANTAB.) M.R.C.P. (LOND.). Pp. 133; 47 illustrations. New York: Oxford University Press American Branch, 1929. Price, $3.50.

*Child Health and Character.** By ELIZABETH M. SLOAN CHESSER, M.D. Pp. 204; New York, Oxford University Press, 1928. Price, $1.50.

*Tumors Arising from the Bloodvessels of the Brain.** By HARVEY CUSHING and PERCIVAL BAILEY. Pp. 219; 159 illustrations. Springfield, Illinois and Baltimore: Charles C. Thomas, 1929. Price, $7.50.

*Physician and Patient.** Edited by L. EUGENE EMERSON. Pp. 244. Cambridge, Mass.: Harvard University Press, 1929. Price, $2.50.

Trabajos y Publicaciones de la Clinica, Volume 4, 1928. By PEDRO DEL ESCUDERO. Pp. 573; 91 illustrations. Buenos Aires: El Ateneo, 1929.

*Morphologic Variation and the Rate of Growth of Bacteria.** By ARTHUR T. HENRICI, M.D. Pp. 194; 36 illustrations. Springfield, Illinois and Baltimore: Charles C. Thomas, 1929. Price, $2.50 paper; $3.00 cloth.

Qualitative and Volumetric Analysis for Medical Students. By H. LAMBOURNE, M.A., M.Sc., F.I.C., and J. A. MITCHELL, M.Sc. Pp. 64; 1 illustration. New York: Oxford University Press, American Branch, 1929. Price, $1.50.

*William Harvey.** By ARCHIBALD MALLOCH, M.D., M.R.C.P. (LOND.). Pp. 103; 13 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

*Handbook of Microscopical Technique.** Edited by C. E. MCCLUNG, PH.D. Pp. 495; 43 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $8.00.

Medical Clinics of North America. Philadelphia number, January, 1929. Pp. 295; 30 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*Growth.** By WILLIAM JACOB ROBBINS, SAMUEL BRODY, ALBERT GARLAND HOGAN, CLARENCE MARTIN JACKSON, CHARLES WILSON GREENE. Pp. 189; 83 illustrations. New Haven: Yale University Press, 1929. Price, $3.00.

A Handbook for the Diabetic. By ALBERT H. ROWE, B.S., M.S., M.D. Pp. 129. New York: Oxford University Press, American Branch, 1929. Price, $2.50.

Surgical Clinics of North America, Pacific Coast Number, December, 1928. Pp. 277; 118 illustrations. Philadelphia: W. B. Saunders Company, 1928.

Transactions of the American Climatological and Clinical Association, 1928, Volume XLIV. Pp. 205; illustrated. Printed for the Society, 1928.

Transactions of the American Otological Society, Inc., 1928. Volume XVIII, Part 1. Pp. 294; illustrated. Printed for the Society, 1928.

*The Pressure Pulse in the Cardiovascular System.** By CARL J. WIGGERS, M.D. Pp. 200; 48 illustrations. New York: Longmans, Green & Co., 1929. Price, $5.00.

NEW EDITIONS.

History of Medicine. By FIELDING H. GARRISON, M.D., LT. COL. M.C., U.S.A. Fourth edition. Pp. 996; 286 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, $12.00.

Green's Manual of Pathology and Morbid Anatomy. Revised and enlarged by A. PINEY, M.D., M.R.C.P. Fourteenth edition. Pp. 650; 261 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $7.50.

A reliable manual in the English manner, well revised by an active younger man, Dr. Green having died since the publication of the thirteenth edition.

Diseases of the Nervous System. By SMITH ELY JELLIFFE, M.D., PH.D. and WILLIAM A. WHITE, M.D. Fifth edition. Pp. 1174; 489 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $9.50.

Unquestionably one of the leading texts in its specialty, this edition by its rigorous revision and inclusion of the latest research holds its position as a portrayer of the problems of the field as well as a reciter of the known past.

Public Health and Hygiene. By WILLIAM HALLOCK PARK. Second edition. Pp. 902; 123 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $9.00.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Angina Pectoris.—A critical study of 200 cases of angina pectoris was made by MORRIS H. KAHN and JOSEPH BARSKY (*Ann. Int. Med.*, 1928, **2**, 401), who make several rather interesting observations. They contend that angina pectoris presents prodromal symptoms indicative of a process which has existed for years, and this despite the fact that almost 22 per cent of the patients had their first attack before the age of forty years. Arteriosclerotic disease is the most outstanding condition in angina pectoris, although there is no direct etiologic connection between arterial blood pressure and the production of cardiac pain. Rheumatism and diabetes are important, also, in the etiology. The most common physical sign was the rough systolic murmur heard over the primary aortic area, but when systolic gallop rhythm is present, the prognosis is extremely bad. The prognosis, under any circumstance, is worse in those individuals to whom the first attack came late in life as contrasted with those who had attacks at comparatively early decades.

A Mechanism Maintaining the Hyperglycemia of Diabetes.—H. E. HIMWICH, W. H. CHAMBERS, Y. D. KOSKOFF, L. H. NAHUM and M. A. ADAMS (*Proc. Soc. Exper. Biol. and Med.*, 1928, **26**, 120) have an explanation for the persistent hyperglycemia which occurs in diabetes even after starvation. Resting muscle of normal animals liberates lactic acid which, entering the blood stream, reaches the liver, where it is removed from the blood and converted into carbohydrate. In the liver it may be retained as glycogen or, leaving the organ, appear in the blood as glucose. Experimental proof of this was found in fourteen

complete diabetic dogs from whom samples of blood were drawn simultaneously from the femoral artery, the femoral vein, the portal vein and the hepatic vein. It was found that there is greater concentration of lactic acid in the femoral vein than in the artery. There is a greater amount of lactic acid in the femoral artery than in the portal vein and less in the hepatic vein than in either; whereas, in the hepatic vein there is considerably more sugar in the blood than there is in the portal vein. The liver, then, forms carbohydrate from lactic acid derived from the muscle. In diabetics it cannot be retained as glycogen and appears in the blood as glucose, aiding in the maintenance of hyperglycemia of diabetes.

Variations in Monocytic Response to Peroxydase Test.—F. A. McJunkin some five years ago reported that he found no peroxydase-reacting monocytes in the blood of a rabbit, contrary to the statement made by Naegeli, who finds that almost all human monocytes are peroxydase-reacting. More recently F. A. McJunkin (*Proc. Soc. Exper. Biol. and Med.*, 1928, **26**, 55) as a result of the culturing of rabbit monocytes on smears of dry human blood, has found that these cells which were previously negative to the peroxydase test may become positive. He concludes from this that since these rabbit monocytes in tissue cultures by phagocytosis may require peroxydase content, that the mononuclears which are phagocytic may get their peroxydase-reacting granules as do those of the rabbit.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Two Cases of Subarachnoid Hemorrhage.—Waterfield (*Guy's Hos. Rep.*, 1928, **78**, 299) says that a striking feature of these cases was the loss of tendon reflexes, in one in the arms only; in the other in all of the limbs. It has been suggested that the loss of deep reflexes might be the result of the sudden shock produced by the hemorrhage on the nervous system, a condition analogous to the spinal shock following a transverse lesion of the spinal cord. As an alternative explanation it was suggested that it might be due to the spread of the hemorrhage into and along the sheaths of the nerve roots, as presumably also in meningitis the abolition of reflexes follows a similar spread of an inflammatory exudate. The other interesting factor, that of delayed papilledema in certain cases of subarachnoid hemorrhage, is probably due to the hemorrhage acting as

a tumor and causing a general increase of intracranial pressure, whereas in the cases in which papilledema and hemorrhage appear within a few hours of the ictus, or striking force, the cause is a leakage of blood into the subarachnoid sheath of the optic nerve.

Spontaneous Dislocations of the Hip Joint during Early Life.—HART (*Arch. Surg.*, 1928, **17**, 587) says that spontaneous dislocation of the hip joint is a preventable deformity. The mechanism of the development of the dislocation is a disturbance of the normal action of the muscles surrounding the hip joint first emphasized by R. Watson Jones. The disturbance of muscle action may be caused by (*a*) paralyses of anterior poliomyelitis with the development of contractures; (*b*) muscle spasm associated with an infectious process of the hip joint and (*c*) muscle incoördination of congenital spastic paralysis. Flexion adduction and internal rotation of the hip should be considered a dangerous attitude. Spontaneous dislocation of the hip is essentially a condition developing during early life. Treatment of a patient with an established deformity is highly unsatisfactory and frequently the dislocation is a minor deformity compared to associated deformities of other joints. Muscle spasm, which is the disturbing factor during the acute stage of infectious arthritis of the hip joint, should be relieved by skin traction, maintaining the involved extremity in the position of stability, abduction and extension. Bilateral involvement of the hip joint is frequently in the infectious group. Instinctive traction and support by the normal extremity should be prevented since it places the uninvolved hip in the position of instability and favors bilateral involvement of the hip joint.

Varicocele.—CAMPBELL (*Surg., Gynec. and Obst.*, 1928, **47**, 558) claims that the etiology of varicocele is not clear but in most cases varicocele is associated with chronic genital congestion induced by faulty sexual hygiene. Of the 500 cases here reported, 9 of every 10 were between fifteen and thirty-five years of age. Advancing age or marriage symptomatically cure most varicoceles. The right side is but rarely involved. If the lesion is large and of long standing, testicular atrophy is frequently observed. The "bag of worms" feeling elicited on palpation of the pampiniform plexus establishes the diagnosis. Clinically and therapeutically three types of varicocele are recognized: (1) Asymptomatic varicocele, of which the patient is unaware. These are best left alone. (2) Moderate or large-sized varicocele. Its presence is denoted anatomically by scrotal enlargement and symptomatically by a feeling of weight, pain or a dragging sensation either in the testicle or referred to the cord, groin or loin. Operation benefits these cases. (3) Small varicocele which causes symptoms disproportionate to the objective findings. Most varicoceles are of this third type. The patients are broadly grouped as sexual neurasthenics. They are best treated by the institution of common sense sexual and physical hygiene. A scrotal suspensory will relieve many. The suspension operation devised by Vicent is described. It is the procedure of choice because it uniformly relieves pain, while postoperative sequelæ are minimal. Hydrococele and atrophy of the testicle are the most frequent postoperative complications.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY.

Pharmacology Evaluation of Some Digitalis Specialities.—G. JOACHIMOGLU (*Deutsch. med. Wchnschr.*, 1928, **54**, 1585) reports the results of a series of biologic assays of a number of digitalis specialities, using the official frog method. The standard activity for tincture of digitalis established by the German pharmacopeia is 150 to 250 frog doses per cubic centimeter. The results with six of the most widely accepted specialities varied from 33 frog doses to 250 frog doses, 3 of the preparations falling below 125. He calls attention to the fact that this wide variation and the considerable weakness of a number of these specialities is of sufficient importance to warrant the institution of some form of official control of their activity.

Heat Therapy.—BRUNO MENDEL (*Klin. Wchnschr.*, 1928, **7**, 1898) reports the results obtained by himself and his associates from the exposure of cultures of three different strains of highly pathogenic streptococci to temperatures varying from 40.5° to 48° C. for varying periods of time. These temperatures do not destroy the organism but, as determined by animal inoculation with controls of unheated samples of the same strains, they reduce enormously the virulence of the organism. Thus exposures for eight hours at 41.5° and for three and a half hours at 43° reduce the virulence from 10 to nearly 100 fold. Similarly the maintenance by external heat of a body temperature of 41° to 42° C. protects rats effectively against inoculation with virulent cultures of the same unheated streptococci. Such temperatures are well borne without obvious harm for three to four hours or more. The author suggests the possibility of applying this method of reducing virulence particularly of streptococci, to certain conditions in man especially, for example, for the treatment of erysipelas, it being shown that a temperature as high as 50° to 52° may be borne by the skin for a half an hour when produced by means of hot dry air. Such a temperature raises that of the tissues 2 or 3 mm. below the surface of the skin to 47° or 48°. Studies are being carried on to determine the therapeutic value of this procedure.

The Action of Small Doses of Drugs.—K. KOTSCHAU (*Deutsch. med. Wchnschr.*, 1928, **54**, 1586; 1928 **54**, 1631) discusses the well attested fact that many drugs manifest quite different biologic actions in very small doses as compared to those produced by large doses. He points out that this difference is often readily demonstrable upon single organs, isolated structures and even upon such lower forms of life as the muscles of the leech and the cell of yeast. Very small doses almost invariably produce stimulation of functional activity although large doses of the

same drug may be nearly purely depressant. While the size of the dose is perhaps the most important factor in determining the nature of the action to be produced, such other factors as the type of the drug, the structure upon which it acts, the susceptibility of the test object and various other conditions all modify the actions obtained. Studying these various factors the author points out that with suitable conditions the action of most drugs studied when administered in small doses is exerted in the direction of a restoration of the function of the test object toward normal. Since most of the drugs are stimulant in these small doses the action is most readily and most markedly obtained in the presence of conditions which lead to some depression of function. With such small doses as are effective, it is often possible to secure a well-maintained mild stimulation which is not followed by any compensatory depression. Large doses usually produce an initial stimulation which is followed by a degree of depression sufficient to counteract the stimulation so that the net result of their administration is *nil*. Very large doses, on the other hand, frequently produce only brief slight stimulation which is followed at once by a marked and prolonged depression, more than sufficient to counteract the initial beneficial effects. The author believes that these observations are of material importance in therapy but he says that it is often difficult correctly to determine the functional state of the tissues in advance so that it is frequently difficult to be certain whether beneficial effects can be obtained by the use of small doses of suitable drugs. Finally, he points out the relation between these observations and certain of the ideas crudely and unscientifically reached by homeopathy.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

The Metabolism of Undernourished Children.—WANG, HAWKS and KAUCHER (*Am. J. Dis. Child.*, 1928, **36**, 1161) studied the caloric and nitrogen balance of normal and undernourished children on high- and low-protein diets. They found that the caloric loss in the urine varies directly with the protein output and therefore with the protein intake. The ratio of calories to nitrogen in the urine also varies directly with the protein intake. They found that the nitrogen retention was directly proportional to the nitrogen intake. The percentage utilization of the calories in a patient on the low-protein diet was greater than in one on the high-protein diet. This is due to the higher coëfficiency of digestibility of the food mixture of the low-protein diet. Underweight children seemed to utilize the nitrogen of a low-protein diet more efficiently than did normal children. A striking gain in weight followed an increase in the proteins in the diet even in normal children, this is especially marked in undernourished children. A diet containing 4 gm. of protein

per kilogram of body weight is their recommendation for undernourished children. They also recommend that the diet of all children normal or underweight should contain one quart of milk. They believe that this is necessary on account of the protein content of this food as well as its content of calcium and vitamin.

Tumors of the Spinal Cord in Childhood.—Stookey (*Am. J. Dis. Child.*, 1928, **36**, 1184) presents a study of 165 verified tumors of the spinal cord for which operation had been performed in the period between 1910 and 1926. Eight tumors were found in children twelve years of age or under. Two of these were operated on before 1922 and 6 after that time. The incidence of the tumors of the spinal cord in this series was 5 per cent of the cases. Tumors of the meninges and of the nerve roots, which are more common in adults, were absent in this series of children. Tumors of the spinal cord in children are classed in two groups; intramedullary group and an extradural group. Tumors of the first group vary in their pathological process and are likely to be tumors arising from congenital rests within the neural tube, the second group are usually sarcomas or fibrosarcomas. The average age of the children in the intramedullary group was eleven years. The average age of the children in the primary extradural group was nine years and the secondary extradural group was three years. The most frequent levels of the involvements were the lower cervical and upper thoracic segments. Extreme variability in the presenting symptoms was found, even with tumors in approximately the same segmental level. Pain either general or localized was not found over the vertebral column. Bladder and rectal disturbances were rare and occurred only late in the cases. Lumbar puncture with withdrawal of fluid may be a valuable aid by causing an increase of sensory signs already present, or it may permit a sensory level to be established which could not previously have been determined. The lumbar manometric test was invaluable. Without it the diagnosis of tumor of the spinal cord could not have been made in half of the cases reported. Stookey recommends a routine manometric test wherever disease of the spinal cord is suspected. He also feels that where there is any doubt as to the diagnosis of tumor of the cord exploration should be done as the operative results are satisfactory and the mortality is low, no deaths occurred in his entire series.

The Chlorid, Sugar and Calcium Contents of Cerebrospinal Fluid in Children.—Neale and Esslemont (*Arch. Dis. Child.*, London, 1928, **3**, 243) studied the sugar, chlorid and calcium contents of the cerebrospinal fluid of 12 children suffering from various diseases without meningeal involvement and he found that these were within normal limits except that in acute pneumococcal infection a subnormal chlorid content was present. They criticize the common view that tuberculous meningitis is constantly associated with a low-chlorid content in the cerebrospinal fluid. It is very essential that the stage of the illness when reading biochemical results be known. The authors draw comparisons between the chlorid content in tuberculous meningitis and other forms of meningitis when examinations were made at frequent intervals. During the course of the illness, curves of the results show special features in each kind of disease. The tuberculous cases show a fall in the early stages

and a rise in the later stages. Pneumococcal cases showed a progressive fall toward the fatal termination. Meningococcal cases showed a similar fall when the disease was fatal but in the cases that became convalescent there was an elevation to within normal limits. The sugar curve in tuberculous meningitis is similar to the chlorid curve in the same cases. In fatal meningococcal and pneumococcal meningitis a progressive diminution in the sugar content of the spinal fluid occurred. In patients recovering from meningococcal infection, the sugar content at first falls and later is followed by a gradual rise to normal. From this, it would be seen that a rising sugar curve is suggestive of improvement. In nonmeningitic and meningitic cases the amount of chlorid in the cerebrospinal fluid varies to some degree with that in the blood. The authors made a number of observations on the calcium in the cerebrospinal fluid. In nonmeningitic cases the calcium concentration is normal. In conditions in which inflammatory change takes place in the meninges, the calcium was usually above the normal level and this was more marked in the suppurative types of meningitis. They found no calcium deficiency in patients having convulsive seizures with the meningitis.

Mechanism of Labor from the Neurologic Point of View.—CROTHERS (*J. Am. Med. Assn.*, 1929, **92**, 99) feels that as long as the tentorium and falx are intact the medulla is unlikely to be exposed to injury. It is generally recognized that abrupt or very severe pressure is likely to rupture this essential barrier to the effects of pressure. If rupture occurs, a sudden release of force drives the medulla into the foramen magnum. Impaction may kill the fetus at once or render it unable to initiate respiration.

In addition, there is the likelihood of vascular injury. Since most of the venous channels are surrounded by the folds that form the dural septums, profuse hemorrhage may occur. The vein of Galen is particularly exposed to danger.

Can Intracranial Birth Injuries be Prevented?—EHRENFEST (*J. Am. Med. Assn.*, 1929, **92**, 97) states that tentorial tears are signs, not so much of excessive force but of the fact that this force has been exerted in a particularly unfavorable direction. Serious dural injuries might be looked for if extraction is done at a time when the position of the head precludes an entirely appropriate application of the forceps. Undue haste in the extracting of the head and especially in the aftercoming head in a breech labor undoubtedly gives a risk to the fetus which is usually greater than the risk that hasty intervention intends to overcome. It has been shown that out of every hundred newborn infants who are born dead or who die soon after birth, seemingly as the result of asphyxiation, between 70 and 80 actually succumb to intracranial lesions. There is only one logical deduction from this and that is that infants who do not breathe properly should be considered as having probably incurred intracranial trauma. This must necessitate the very gentlest procedure in attempting its resuscitation. The methods of swinging the baby or of suspending the baby by its legs are seen to be the worst possible manipulations in the presence of trauma intracranially.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Potassium and Calcium Balance in the Blood Serum in Dermatoses.—NATHAN and STERN (*Arch. f. Derm. u. Syph.*, 1928, **156**, 446) found no distinctive calcium or potassium values for the blood serum of patients with a variety of dermatoses, which could be regarded as of etiologic significance. The changes which occurred were conditioned rather by the acuteness, intensity and prolongation of the inflammatory process in the skin. In dermatoses of the erythema type, at the height of the disease, a drop in potassium and a rise in serum calcium often takes place, the balance being restored as symptoms disappear. In dermatoses associated with edema, there is at onset a rise in potassium and not infrequently a drop in calcium, which with rapid disappearance of the edema is followed usually by subnormal potassium values. It appears that the rise in potassium is associated on the one hand with the action of protein bodies, on the other with the biochemical changes preceding edema, and is therefore to be regarded as merely an accompaniment of the cutaneous manifestations. There are undoubtedly dermatoses in which definite disturbances in the vegetative nervous system are associated with definite and prolonged changes in the mineral balance of the blood serum, but these have symptomatic significance only. The assumption that a primary disturbance of mineral metabolism is the basic etiologic fact of any dermatosis is as yet unproven.

Rôle of the Sympathetic Nervous System and the Calcium-potassium Ratio in Altering Cutaneous Irritability in the Rabbit.—KLAUDER and BROWN (*Arch. Dermat. and Syphilol.*, 1929, **19**, 52), continuing their studies of calcium metabolism in the skin, find that their observations on the increase of cutaneous irritability coincident with a rise in potassium content; and of a decrease in potassium with a rise in calcium content, has been confirmed by Toyama and Hayashi. The important phenomenon is not so much the absolute change in mineral content as a change in the ratio between these two metals. The sodium tends to follow the potassium changes. The authors were unable to correlate the hydrogen-ion concentration of the rabbit skin with its irritability or with the calcium-potassium ratio. Following the observations of Howell, Zondek and others, the authors proceed in this study to apply the concept of calcium-potassium balance in relation to the sympathetic-vagus control of cellular irritability of the heart muscle, to the behavior

of the skin. They induced disturbance of the vegetative nervous system of rabbits by pharmacologic methods, including the intramuscular injection of atropin sulphate, ephedrin hydrochlorid, pilocarpin, cholin hydrochlorid, and histamin and then by means of an indicator reaction, so to speak, consisting of the response of the animal's skin to various dilutions of croton oil, they measured the degree of inflammatory response. They then determined the calcium-potassium ratio in the entire skins of the animals after death, and found that though the actual degree of change was within the limits of experimental error of the methods, the changes in balance occurred in the expected direction. Ephedrin, atropin and pilocarpin all caused a reduction in the irritability of the skin in the majority of the animals treated, and a rise in the proportion of calcium to potassium in the skin. There were, however, notable differences in certain of the animals, which the authors do not discuss in this paper. Control animals showed little or no variation. Capillary dilatation or constriction is not apparently the cause of the altered reactivity of the skin in the experimental animal, for the vasodilator drugs, cholin and histamin were without effect on the cutaneous reactivity.

Mycotic Inguinal Lymphadenitis Associated with Superficial Fungus Dermatitis of the Feet.—WHITE (*Arch. Dermatol. and Syph.*, 1928, **18**, 271). The fungus, Trichophyton interdigital, was recovered both from the primary focus between the toes and from swollen lymph nodes in the groin. There was no visible lymphangitis of the leg. The results of microscopic direct study were confirmed culturally.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Irradiation of Cervical Cancer.—The results of a careful follow-up study in cases of cancer of the cervix are always of interest to the gynecologist and probably no clinic has a more detailed and personal postradiation follow-up clinic than that of the Woman's Hospital in New York City, where, according to WARD and FARRAR (*J. Am. Med. Assn.*, 1928, **91**, 296), one of the two of them observed the cases of cancer of the cervix which have been irradiated once a month over a period of five years. In 1925 they reported their results in two five-year series of cases treated by radium therapy. Their percentage of cures in all cases, based on the cases they had traced, was 23.6 per cent

and the early and borderline cases it was 52.9 per cent. They have completed two more five-year series and are now able to report on all patients treated in 1919, 1920, 1921, 1922 and in the first five months of 1923. For the benefit of the skeptical members of the profession it is of interest to note that all of their records have been audited and the statistical figures compiled by professional statisticians and have been certified by them as correct. Following Schmitz's classification, the following table shows the five-year end results from the use of radium in primary cancer of the cervix:

	Treated.	Traced.	Living.	Per cent living of cases.	
				Traced.	Treated.
Classes I, II, III, IV	134	126	31	24.6	23.1
Classes I and II (limited to cervix)	32	30	17	56.7	53.1

A comparison of these results with the statistics of seventeen clinics as given by Heyman in his report, and also with the results obtained by Forsell and Heyman at the radium clinic in Stockholm, is given in the following tables:

COMPARATIVE RESULTS OF OPERATION AND RADIUM TREATMENT.

	Per cent cured.
All clinical:	
Operative treatment	18.0
Radiologic treatment	16.3
Radiumhemmet (Stockholm)	22.4
Woman's Hospital, May, 1928	23.1
Primary mortality:	
Radical operation	17.2
Radiologic treatment	2.0
Operable Cases Only.	
All clinics:	
Operative treatment	35.6
Radiologic treatment	34.9
Radiumhemmet	44.4
Woman's Hospital, May, 1928	53.1

As a result of their study into this subject they conclude that after the first irradiation in carcinoma of the cervix, every patient should be examined each month for a period of at least five years and as much longer as possible, since repeated irradiation when needed checks the extension of the carcinoma. A daily douche and care of the general health are necessary adjuncts for a cure. They believe, and we surely agree with them, that the statistics today show that in irradiation of early carcinoma of the cervix there are just as good results to be obtained as in the radical operation, with less primary mortality and less morbidity. In discussing this paper, Curtis said that the public has a firmly entrenched belief that cancer of the uterus is an essentially hopeless disease, and we, as specialists and experts, are entirely too prone to agree with this incorrect and pessimistic attitude. He has been increasingly impressed with the value of diathermy which greatly increases the number of apparent cures, and he believes that it promises to displace radium in the treatment of a considerable number of selected cases.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Leber's Optic Atrophy and its Relationship with the Heredofamilial Ataxias.—FERGUSON and CRITCHLEY (*J. Neurol. and Psychopath.*, 1928, **9**, 120) draw attention to the existence of an atypical variety of Leber's disease wherein positive neurologic signs were present in addition to the optic atrophy. In four persons, all of the same family, the onset occurred at puberty, optic neuritis leading to optic atrophy, fields with central scotomata and the course of the disease all typical of Leber's optic atrophy. In two members, the condition was uncomplicated. One member also showed some degree of mental defect and infrequent epileptic attacks, features which may occasionally be present. The fourth patient showed in addition to the characteristics of Leber's atrophy, the development of additional features of pyramidal disease, ataxis and sensory loss. The author postulates four groups: (1) Simple, uncomplicated heredofamilial optic atrophy; (2) familial optic atrophy in persons whose family shows a neuropathic tendency, migraine, or epilepsy; (3) optic atrophy and neurologic signs coëxisting, both appearing (*a*) early in infancy, (*b*) in early adolescence; (4) optic atrophy with heredofamilial ataxias of Marie. The association of neurologic findings may contribute to the knowledge of the etiology of Leber's disease, by suggesting that the essential pathologic process is a neuronic abiotrophy, limited, in typical cases, to the optic nerve.

Changes in the Fundus and in the Blood pressure in the Retinal Arteries in Increased Intracranial Pressure: Papilledema and Optic Atrophy.—BERENS, SMITH and CORNWALL (*Arch. Neurol. and Psychiat.*, 1928, **20**, 1151) report that papilledema is frequently a late, rather than an early sign of increased intracranial pressure, and may be absent in the presence of hypertension of long standing. From clinical, pathologic and experimental studies of the pathogenesis of papilledema, the most important factors in its production appear to be mechanical blocking of the lymphatic drainage by pressure of the cerebrospinal fluid on the optic nerve and the lymphatic channels which surround the central artery of the retina. Mechanical obstruction to venous outflow is possibly a less important factor in the production of hemorrhages and exudates. When papilledema is established, the observations on the retinal blood pressure may be misleading as to indicate a low intracranial pressure in certain cases when the intracranial pressure actually is high, no explanation is given for this. Baillart's method for determining the diastolic and systolic blood pressure in the central artery of the retina is valuable to the trained observer in spite of inaccuracies. The author's observations in a series of eleven subjects who were examined in the sitting position by Baillart's method, showed an average blood

pressure in the brachial arteries of 118 systolic and 76 diastolic; the intraocular pressure averaged 17 in the right eye and 17.5 left eye; the retinal blood pressure in the central artery averaged 68.2 systolic, 32.2 diastolic right eye and 67.4 systolic, 32 diastolic left eye. These figures are lower than obtained by others using the same method. A marked increase in retinal diastolic pressure was noted when the subject changed from standing to the prone position. Jugular compression caused a marked increase in cerebrospinal-fluid pressure, which was accompanied by a marked rise in diastolic pressure in retinal arteries in 4 patients. When a diagnosis has been made the method aids in making possible observations on augmentation and remission of pressure.

RADIOLOGY

UNDER THE CHARGE OF

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Cholecystography.—From a series comprising 625 patients of whom 100 were operated on, WATKINS and MILLS (*Radiology*, 1928, **11**, 91) conclude that approximately one-half of the patients referred for gastrointestinal examination reveal evidence of functional disability of the gall bladder, and such evidence is quite reliable. On the other hand, a diseased gall bladder may function normally; in approximately 30 per cent of the patients who were proved by operation to have cholecystic disease the response to the Graham test was normal.

Treatment of Hyperthyroidism.—The present-day treatment of hyperthyroidism does not attain ideal objectives, states ROSE (*Am. J. Roent. and Rad. Therap.*, 1928, **19**, 546). Since the ultimate factors responsible are not known, treatment remains empirical and too often merely breaks a link in the etiologic chain; consequently residual symptoms or recurrences occur all too often. The ideal treatment should entail a minimum amount of immediate risk; it should produce a maximum percentage of patients economically and socially restored with a minimum of residual symptoms; it should involve the least possible loss of time and earning power during its application; it should be followed by a minimal number of recurrences; its effects should be apparent in the shortest possible time; it should be effective in checking permanently the complications of hyperthyroidism, particularly heart disease; it should be available to the average majority as well as to the expert few. Medical treatment consists largely in "skillful neglect." It has been credited with as high as 83 per cent of cures, and its mortality is approx-

imately the same as the surgical average, though probably higher than that of the larger surgical clinics. However, it requires months or years, is ineffective in checking visceral damage, cardiac disease in particular, and does not appear desirable in most cases in view of the reported efficacy of surgery or radiation. Radiation is popular, but few careful statistical analyses of the final results in after years have been reported. It eliminates immediate risk, is easily carried out, and interferes little with the patient's mode of life. On the other hand, it is ineffective in arresting cardiac and visceral complications, recurrence is probably more likely than after surgical treatment, and the duration of treatment is prolonged. Surgery is the most popular single method. Judd and Pemberton have reported more than 79 per cent of cures after five or six years. It has the advantages of greater effectiveness in arresting cardiac disease, prompter appearance of improvement, and fewer recurrences. Conversely, its immediate mortality, though low, is greater than from irradiation, and postoperative accidents and complications may occur. Rose then relates the experience of the thyroid clinic at the University of Pennsylvania Hospital and concludes: (1) The so-called medical treatment of hyperthyroidism is inferior to surgery and radiation, and should not be used alone unless the patient declines specific treatment. (2) Medical supervision in association with surgical or radiation therapy is of the greatest importance, particularly in relation to visceral complications. (3) Removal of active harmful foci of infection should accompany or precede any type of treatment selected. (4) A trial with radium or Roentgen rays is indicated: (*a*) In mild or acute cases of hyperplastic type without complication, where a three to four months' period of observation is economically possible and without risk to the patient. (*b*) In cases of any type which are considered bad surgical risks; in these subsequent operation can often be successfully performed. (5) Surgical treatment is indicated: (*a*) In all frankly adenomatous goiters with hyperthyroidism. (*b*) In all cases of hyperthyroidism with visceral complications. (*c*) In all cases which have not responded satisfactorily to irradiation after four to six months. (6) Until more convincing statistical proof of the ultimate efficacy of irradiation is offered, surgery must be considered, in general, the most satisfactory type of treatment for hyperthyroidism.

Roentgen Therapy in Bone Tumors.—Irradiation in the form of deep Roentgen ray therapy, according to EVANS and LEUCEUTIA (*Am. J. Roent. and Rad. Ther.*, 1928, **20**, 303) should find a more extensive application in all forms of bone sarcoma and giant-cell tumor, operable or inoperable, whether in combination with surgical measures, mixed toxins or the more recent lead therapy. "Five-year cures" are possible even in cases with extensive metastasis and where no other form of treatment could be of benefit. Cellular tumors, without much stroma and rich in blood supply, though clinically very malignant, may be made to disappear entirely by irradiation. Tumors rich in mature intercellular structure (cartilage, bone) and poor in bloodvessels, may prove entirely refractory to irradiation, while surgical procedures may lead to excellent results. In tumors of the intermediate type, a marked sclerosis with considerable prolongation of life often results from irradiation.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Mental Hygiene and the Physician.—HERMAN M. JAHR (*Arch. Pediat.*, 1928, **45**, 491) calls attention to the marked popular advance of mental hygiene concepts and the difficulty the physician has in keeping pace with this advance. He feels that the pediatrician especially should keep in touch with progress made in the field of preventive work in mental diseases in order to properly advise mothers concerning the mental hygiene of the patients in their care. He believes that the preservation of physical health manifested as a result of modern pediatric practice might be paralleled by similar care in behavior disorders of childhood in the preservation of mental health. He cites a number of instances in which mental hygiene concepts have been of service to him and states that the physician should consider the child as a whole and not as individual organs or as an isolated physical body.

Ueber kongenitale Wortblindheit.—KARL MAYER (*Monatschr. f. Psychiat. u. Neurol.*, 1928, **70**, 161) presents a case with very detailed analysis of the relationship of this disease to other forms of focal disturbances of a similar character. Aside from the carefully worked out details of his case he presents two things of considerable value. One of these is a table of comparison between the findings in congenital word blindness and acquired word blindness. Stress is laid here on the differences in the presence or absence of ability to write spontaneously, to write from dictation, to copy, the presence or absence of hemianopsia and knowledge of colors. Another useful thing is a sample scheme for diagnosis and analysis of congenital word blindness covering the principal investigation necessary in a schematic form. He reviews the literature quite thoroughly and discusses the theories of etiology. His own opinion seems to be that those who are congenitally word blind represent a philogenetically archaic human development comparable to the level of hieroglyphic writing and reading. He recognizes the similarities between congenital word blindness and the acquired form and the suggestion therefrom that these conditions represent a focal aplasia of the angular gyrus occurring either through birth injury or congenitally. The pathology, he states, cannot be definitely established in the absence of pathologic studies. In his own case he finds that difficult birth might have permitted brain injury. However, he finds difficulty in accepting this as the cause in view of the fact that there was a marked familial tendency to intellectual defects. An uncle and a brother of the patient are idiots, a sister attends a special school, the mother showed marked

disturbances of writing and the patient himself showed marked defects in his emotional life to the extent of a long series of delinquencies. The author takes issue with those who would interpret these conditions in the sense of idiocies because he feels that the diagnosis of imbecility or idiocy cannot be made upon a single defect but must be based upon a generalized deficiency in the entire personality. His own patient showed a very slight deficiency in intellectual capacity.

Ueber die Behandlung der tabischen Optikusatrophie mit Lufteinblasung.—L. HORN and H. KOGERER (*Ztschr. f. Augenheilk.*, 1928, **64**, 377) report 5 cases of tabetic optic atrophy treated with suboccipital air injections. Four cases were treated with neosalvarsan as well, and one case was treated with malaria, in addition to the air injection. The authors find definite improvement in vision in 3 of the first 4 cases reported. In 2 the improvement was permanent, in one it was only transitory. The fourth case showed no improvement whatever. The case treated with malaria showed a permanent improvement also. The authors attribute the favorable results to the removal of toxins with the spinal fluid and to the setting up of local reaction by the irritation of the air. Since the tabetic atrophy is not reversible and since the cases show improvement with no absolute relief the authors feel that toxic substances in the cerebrospinal fluid are probably responsible for a portion of the visual defect. (The series is too small to have any very great significance and requires carefully controlled check experiments. One case showed a decrease of spinal fluid cells from 112 to 18 after air injection, a most astounding result!)

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Immunity and Allergy in Tuberculous Infection.—WORINGER and ADNOT (*Compt. rend. Soc. de biol.*, 1928, **99**, 849) found that the skin exposed to ultraviolet rays on one side of patients with tuberculosis gave a lessened cuti-reaction to tuberculin as compared to the reaction in the skin of the other unexposed side. Since ultraviolet rays are known to augment the immunity the authors consider the above results to be evidence that allergy and immunity are two quite distinct functions both arising from the tuberculous infection but obeying different laws and certainly differing in their significance. It is, therefore, not possible to estimate the condition of immunity in a patient by the allergic reaction.

Spread in the Air of Oral Bacteria by Droplets.—It has been thought that the spray of fine particles from the oral cavity in coughing rapidly evaporates and leaves in the air dried bacteria from the droplets. Experiments carried out by HAUN (*Ztschr. f. Hyg. u. Infectionskrankh.*, 1928, **108**, 613) are against the view that this drying is of any practical importance in the spread of bacteria from mouth to mouth. Artificial sprays of suspensions of Bacillus influenzæ and Bacillus prodigiosus gave much smaller droplets than are produced in coughing and even these small particles remained as droplets for at least half an hour. The author believed then, that rapidly drying does not take place but that the large particles from coughing do not remain as long in the air on account of their size as the droplets used in his experiments. The author states, but brings little to support his view, that a fall in room temperature, the humidity or the air movements would not change his results but since he is considering only the early evaporation this has little bearing on the problem of sputum droplets remaining in the air in cold and moist climates and the influence these may have on the spread of respiratory infections.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Experimental Black Tongue of Dogs and its Relation to Pellagra.—GOLDBERGER and WHEELER (*Pub. Health Repts.*, 1928, **43**, 172) make an extensive report on a disease of dogs which is of interest in human pathology because of its similarity to pellagra of man. The summary and conclusions are as follows: (1) A pathologic condition has been induced experimentally in the dog by feeding (*a*) a type of diet observed in association with pellagra and also (*b*) a diet previously found by experimental test in the human subject to be a pellagra-producing diet. (2) A description of the experimental disease summarizing observations extending over a period of nearly five years is presented. (3) The experimental condition is clinically and postmortem indistinguishable from the spontaneous disease of dogs known as black tongue or Stuttgart dog epizoötic, and it is concluded that they are identical. (4) On the basis of the similarity of clinical manifestations it is considered highly probable that experimental black tongue and the Chittenden-Underhill pellagra-like syndrome in dogs are identical. (5) An eruption restricted to the scrotum occurring in experimental black tongue, which in certain

of its distinctive features is indistinguishable from the dermatitis of pellagra, is considered as constituting, at least in conjunction with the other points of resemblance, well-night conclusive *clinical* evidence of the identity of the two conditions, black tongue and pellagra. Further evidence to the same effect is found in the suggestion of a common etiology indicated by the successful experimental production of the disease in the dog by feeding with pellagra-producing diets.

Tetanus following Vaccination against Smallpox and its Prevention (With Special Reference to the Use of Vaccination Shields and Dressings).—ARMSTRONG (*Pub. Health Repts.*, 1927, **42**, 3061) made epidemiologic observations on a total of 98 cases of tetanus following vaccination occurring within recent years. The one factor common to all cases was the presence of a dressing of some sort on the vaccination wound at some time during the course of the vaccination. Special shields, gauze dressings and bunion pads were used in the great bulk of the cases. In a study of the method of insertion it was found that large abrasions had been made in about two-thirds of the cases. The combination of the large insertion and the dressing seemed to be extremely favorable for the development of tetanus. On the experimental side it was found that, using rabbits and monkeys, it was easily possible to induce postvaccinal tetanus if a shield or dressing was tightly applied over the little wound. On the other hand, in the absence of shield or dressing it was extremely rare to have tetanus develop. The suggestions for the prevention of postvaccinal tetanus are substantially as follows: No dressing of any sort is to be applied to the wound, but it is to be kept cool and dry. The insertion should be small, never more than $\frac{1}{8}$ inch in its greatest diameter, and, preferably, the use of a method which does not remove the epidermis. Acetone is suggested for cleansing the skin, and utmost gentleness in its application is enjoined. Vaccination on the leg is regarded as objectionable. It is recommended that vaccination is best performed during the first year of life. This is thought to be distinctly better than at the time of entrance to school, as is the general practice at the present time in this country.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF JANUARY 21, 1929.

Extension Reflex from the Knee.—G. P. MCCOUCH, AND B. J. ALPERS. (from the Laboratory of Physiology, University of Pennsylvania). Evidence is presented for the existence of an ipsilateral extension reflex which may be elicited from the subpatellar bursa by either mechanical

or electrical stimulation. The reflex has been analyzed by synchronous mechanical and electric records taken under isometric conditions from the quadriceps femoris in decerebrate cats. The response to repetitive induction shocks of moderate frequency applied to the subpatellar bursa or to the articular twig of the recurrent articular branch of the peroneal nerve is characterized by long, latent, gradual recruitment to a rather low plateau tension, long after discharge, and absence of rhythm of stimulation in both tension curve and electromyogram. Evidence is presented which suggests that the reflex is concerned in the production of rebound. Extensor reflexes elicited from the internal saphenous nerve above the branches to the knee approximate more closely to those described by other observers from stimulation of the sciatic. The presence of the rhythm of stimulation in these records is ascribed to the presence of afferents of the flexion reflex, which are believed to inhibit repetitive discharge of the center.

The Thermal Conductivity Method of Gas Analysis.—L. E. Bayliss (from the Department of Physiology, University College, London). Analysis of gas mixtures by the method of determining their thermal conductivity has certain advantages over the more usual chemical methods in that it gives continuous records, often without any loss or destruction of the gas, and is rapid. The apparatus has been developed by Shakespear and by Daynes,[1] in England, and by Palmer and Weaver,[2] of the Bureau of Standards in the United States, and the principle on which it works is that the temperature of a heated platinum wire depends upon the thermal conductivity of the gas surrounding it, so that, if the heating current remains constant and convection is avoided, the resistance of the platinum wire will depend only on the composition of the gas. Accordingly, the circuit used is essentially that of the ordinary Wheatstone bridge and the galvanometer, which need not be a very sensitive one, can be used either as a deflection instrument or as a null-point instrument. In the first case, of course, the composition of the gas is read off on the galvanometer, and in the second on the compensating resistance, and in both cases empirical calibration is required. The total current in the circuit must be kept accurately steady at a predetermined value, so that a good ammeter is required. The measurements are independent of barometric pressure and of temperature, within limits.

For biological purposes mixtures of CO_2, oxygen and nitrogen are of particular interest, and the thermal conductivities of these gases is such that the percentage of CO_2 may be determined in mixtures of the other two so long as the variations in the percentage of oxygen do not exceed eight times the accuracy desired in the measurement of the CO_2. Conversely the content of oxygen can only be determined if the CO_2 is either removed previously, or held constant within the above-defined limits. Water vapor must also either be removed or held constant, since its thermal conductivity is about twice that of oxygen.

The accuracy obtainable is about 0.02 per cent, both of CO_2 and oxygen. If the sensitivity is pushed much further difficulty is experi-

[1] Proc. Roy. Soc. Lond., 1920, **97A**, 273.
[2] Technologic Papers, Bureau of Stds., 1924, No. 249.

enced with shifting zeros, owing to variations in room temperature and total current in the bridge, but they can be minimized in the case of CO_2 by arranging to have a compensating gas of approximately the same thermal conductivity in the other chamber, and in the case of oxygen, by using a mixture of hydrogen and oxygen. In the latter case it is probable that a sensitivity of 0.001 per cent would be attainable.

The great value of the thermal conductivity method is shown chiefly in the determination of metabolism, and an apparatus incorporating it has been described by Bayliss, Müller and Starling.[3] The principle of their method is to remove the CO_2 and add oxygen to the closed circuit respiratory system just so fast as the one is being added to it and the other removed by the animal or isolated organ under study, the oxygen being generated electrolytically, so that the rate of addition can be instantly varied over wide limits, and the amount added in a given time estimated from the total quantity of electricity passed through the generator. Their circuit can be simplified, however, by using a pump of known stroke output to circulate the respiratory gas through the soda-lime tubes. Since the percentage of CO_2 is known continually, the amount absorbed in any time can be at once calculated from the total volume of gas sent through the absorption tubes in that time, and this can be determined by counting the strokes of the pump. Ozone can be removed from the oxygen generated electrolytically by coating the platinum anode with platinum black and then heating to redness. If the coating is left black considerable quantities of oxygen are adsorbed, the exact amount depending upon the current flowing, so that every change results in a temporary departure of the actual rate of generation from that calculated from the current, oxygen being kept back if the current is raised and given off excessively if it is lowered. It is better, also, to connect a separate electrolytic generator in series with the main oxygen generator, and to collect both the hydrogen and oxygen evolved from it in a gas burette. The volume of gas to be measured is thus three times that of the oxygen, and the level of the fluid in the main generator is not altered by small pressure differences introduced by the gas burette system.

Relation of Size of Dose to Development of Morphin Tolerance.—C. F. Schmidt and A. E. Livingston (from the Laboratory of Pharmacology, University of Pennsylvania). Four dogs given 2 mg. per kilo of morphin daily showed no trace of tolerance on the twenty-sixth day, but when the dose was increased to 10 mg. per kilo they became tolerant within a week. Two dogs kept on 2 mg. per kilo daily ceased vomiting in the eighth week, showed briefer narcosis in the tenth, but were maximally tolerant only after the thirteenth week. Six dogs on 10 mg. per kilo daily also failed to become tolerant rapidly; 3 survived; all vomited until the fifth week, showed decreasing narcosis after the sixth but were not tolerant after seventeen weeks. Two were then raised to 30 mg. per kilo, and tolerance appeared within a week. The third, kept on the 10-mg. dosage, developed maximal tolerance about the twentieth week. Evidently dogs do not readily become tolerant to small daily doses of morphin.

[3] Jour. Physiol., 1928, **65**, 33.

On 30 mg. per kilo daily 1 of 3 dogs survived; vomiting ceased on the tenth day, narcosis was distinctly less on the fifteenth day and tolerance was maximal in the fourth week. A normal dog given an initial convulsant dose of morphin (100 to 250 mg. per kilo) is subsequently highly resistant to the narcotic effects of 10, 30, 50, 60 even 120 mg. per kilo of morphin. This "acute tolerance"[1] previously noted by Claude Bernard[2] and by Tatum[3] has been studied in 12 dogs which survive after seven to nineteen months, during which none of them was ever prostrated by the daily dose, and none of them which had survived the convulsant period failed to survive the subsequent daily injections; control dogs showed a mortality of 50 per cent or more upon such daily doses. The degree of tolerance exhibited by dogs after recovery from morphin convulsions is very high to the narcotic but very low to the gastrointestinal effects. Upon continued administration of the same dose the tolerance to the narcotic effects increases little, if at all, but the gastrointestinal effects disappear within two weeks, after which the animal responds exactly like one which had been gradually brought to the same dosage.

Apparently tolerance to morphin is induced in the dog only very slowly when the tissue concentration of morphin is low, more rapidly if the concentration is increased or is higher from the start, and, as far as the narcotic (cerebral) effects are concerned, within twenty-four hours if the animal is given an initial overwhelming dose. Since it has been demonstrated recently by Wolff[4] that excretion of morphin by tolerant dogs is not significantly different from that by normal animals, the difference must be due to a change in tissue reactivity to morphin.

We have demonstrated[1] the decreased circulatory response to morphin in chronically poisoned and "acutely tolerant" dogs. This result is unaltered by decentralization or by destruction of the central nervous system, so that the theory of Tatum[3] cannot explain the circulatory phenomena, and one must assume the presence of cellular resistance or tolerance in bloodvessels of dogs chronically or acutely poisoned by morphin. The depressant effects of morphin injected intravenously, upon respiratory and vasomotor centers of normal dogs rapidly disappear as the injections are repeated; this indicates that certain nerve cells can become "acutely tolerant" to morphin, so that it is not improbable that an initial overwhelming dose could protect other brain cells against the narcotic effects of subsequent smaller doses. We do not know that "acute tolerance" is due to the same mechanism as the tolerance of chronic poisoning, but the result is substantially the same, gastrointestinal effects excepted.

Morphin tolerance in the dog has an all-or-none aspect, in that animals tolerant to small daily doses (2 or 10 mg. per kilo) are affected little or no more by much larger doses (100 mg. per kilo), gastrointestinal effects again excepted. Apparently the gastrointestinal tract is less readily accustomed to morphin than most other body tissues. We

[1] Schmidt, C. F., and Livingston, A. E.: Jour. Pharm. Exper. Therap., 1928, **33**, 284.

[2] Leçons sur les anesthesiques, etc., Paris, 1875, p. 167.

[3] Jour. Pharm. Exper. Therap., 1926, **27**, 237 1927, **31**, 213.

[4] Proc. Physiol. Soc. Phila., December 17, 1928. Am. Jour. Med. Sci., 1929, **177**, 305.

believe that tolerance to morphin in the dog depends largely or wholly upon increased cell resistance to morphin, and has little or no relation to destruction of the drug. Concerning the mechanism of this increased resistance we have no information.

The Production of Isospermatoxins.—C. EISEMAN and M. H. FRIEDMAN (from the Department of Physiology of the University of Chicago). The fact that the incidence of spontaneous isospermatoxins has not been duly considered, that, in general, the dose of antigen employed has not been definitely stated, that an adequate titration of the isospermatoxins heretofore reported has not been carried out, cast in question the alleged ease with which these isoantibodies are produced. Consequently, we designed experiments to define the antigenic dose required to produce isospermatoxin in significant titer. About 4 cc of blood was obtained from each of 4 normal females. In a small serologic tube 0.1 cc of the serum of each rabbit was added to an equal quantity of fresh sperm suspension, made by macerating in saline the epididymis of a vigorous buck killed by a blow on the head. These tubes, together with a saline control in which 0.1 cc. of saline was substituted for the serum, were corked and incubated at 37° C. From time to time a loopful of the fluid was removed for examination in a hanging-drop preparation. At the end of twenty-four hours no motile sperm were found in the saline control, while in each of the sera actively motile sperm were seen at the end of twenty-six hours. On the following day each of these 4 rabbits were injected intravenously with 5,000,000 rabbit sperm. Repeated serologic examinations of the blood of these animals during the subsequent three weeks failed to reveal the presence of any substances capable of immobilizing rabbit sperm when tested in the manner described above

On the assumption that the size of the antigenic dose was too small, and considering the possibility voiced by some previous workers, that the injection of heterologous sperm would provoke the production of antibodies, which would immobilize homologous sperm, we injected one series of 7 rabbits with several doses of rat sperm and another series of 9 rabbits with repeated doses of rabbit sperm. Neither the injection of a total of 247,000,000 rat sperm in twelve injections, nor the injection of 500,000,000 to 1,500,000,000 rabbit sperm in five to ten injections, was followed by the appearance in the sera of the injected animals of a substance which would immobilize rabbit sperm when tested by our method ten days after the last injection.

Adding to each of the sera an excess of fresh complement in no way modify our results. Further, to obviate the possibility that our animals were immunilogically refractive, it was shown that the rabbits developed hemolytic titers of at least 10,000 after injection of guinea-pig corpuscles.

Having only consistently negative results in the rabbit, we were induced to repeat the allegedly successful procedures in the rat, in which the injection of so little as 40,000 sperm intramuscularly resulted in the appearance of isospermatoxin. After the injection of 600,000 rat sperm into a series of female rats we were able to detect in the sera of the injected animals a substance which readily immobilized rat sperm. But in the sera of the uninjected control animals this substance was found also. We were able to demonstrate that this spontaneous

spermatoxic substance was not an artefact, but was *variably* present in the sera of all rats, male or female. Due to the prevalence of Bartonella infection in our rat colony, it was thought that this spontaneous spermatoxic substance might be associated with the infection. This was quickly negated by our finding of the spermatoxic substance in rats obtained from the Wistar Institute and which were demonstrated to be Bartonella-free. It was soon found that this spontaneous spermatoxin was inactive in dilutions greater than 1 to 10 and was completely destroyed by heating at 56° C. for thirty minutes.

Subsequent experiments on Wistar rats permitted the statement that not only the injection of 600,000 rat sperm in three intramuscular injections, but also the injection of 45,000,000 rat sperm in five injections, failed to increase the spermatoxic activity of the sera of the injected animals beyond that found in the sera of normal untreated rats.

As a final resort we turned to the guinea pig. We found that the injection of the whole substance of five tests and epididymes injected intraperitoneally in five injections would produce in the serum of a female guinea pig a thermostable, species-specific isospermatoxin which required the presence of complement for the manifestation of its activity. When titrated against 28,000,000 fresh guinea-pig sperm it was active (complete immobilization of the sperm within one hour) in dilution of 1 to 10, and only slightly active or wholly inactive in dilution of 1 to 50.

Briefly, with our methods we have been unable to support the claims that the intravenous injection of rabbit sperm into female rabbits, and the intramuscular injection of rat sperm into female rats, result in the production of isospermatoxic antibodies. Yet, in the guinea pig we have succeeded in producing such antibody in low titer.

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